RADON-ASSOCIATED LUNG CANCER MORTALITY RISK AT LOW EXPOSURES:

CZECH, FRENCH, AND BEAVERLODGE URANIUM MINERS

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Abbreviations

α Alpha

β Beta

γ Gamma

ALARA Radiation doses are to be As Low As Reasonably Achievable, social and economic factors being taken into account.

BEIR Biological Effects of Ionizing Radiation

BEIR VI Sixth Committee on the Biological Effects of Ionizing Radiation

Bq Becquerel

CCDB Canadian Cancer Database

CEA Commissariat à l'Energie Atomique

COGEMA Compagnie Générale des Matières Nucléaires Inc.

Ci Curie

CI Confidence interval

CMDB Canadian Mortality Database

CNSC Canadian Nuclear Safety Commission

DOF Degrees of freedom

ERR Excess relative risk

Gy Gray

IAEA International Atomic Energy Agency

IARC International Agency for Research on Cancer

ICRP International Commission on Radiological Protection

IRSN L'Institut de Radioprotection et de Sûreté Nucléaire, France

J Joule

LET Linear energy transfer

LLR Long-lived radionuclides

LR Likelihood ratio

MeV Mega electron Volt (of alpha energy)

MLE Maximum likelihood estimate

mSv millisievert

NCRP National Council on Radiation Protection and Measurements

NRC National Research Council

OHSN-REB Ottawa Health Science Network-Research Ethics Board

pCi Picocurie

RDP Radon decay products (radon progeny)

RR Relative risk

SAS Statistical Analysis System software

SD Standard deviation

SIN Social insurance number

SMR Standardized mortality ratio

SURO National Radiation Protection Institute, Czech Republic

Sv sievert

tU Tonnes of uranium

UNSCEAR United Nations Scientific Committee on the Effects of Atomic Radiation

WL Working level

WLM Working level month

Glossary

Concentration: the activity of radon gas in terms of decays per time in a volume of air. The unit of radioactivity concentration is given in Becquerel per cubic metre (Bq/m^3) (WHO 2009).

Equilibrium factor (F-factor): a measure of the degree of radioactive equilibrium between radon and its short-lived radioactive radon progeny. Radon is constantly decaying and giving rise to radon progeny. These are short-lived and decay until reaching a long-lived isotope of lead. The F-factor is used to describe the ratio between radon and its progeny. An F-factor of 1 means equal amounts of radon and its progeny. An F-factor of 0.4 is taken as representative for homes (WHO 2009).

Excess relative risk (ERR): the ERR is an epidemiological risk measure that quantifies how much the level of risk among persons with a given level of exposure exceeds the risk of non-exposed persons (WHO 2009).

Nuclear energy worker (NEW): means a person who is required in the course of the person's business or occupation in connection with a nuclear substance or nuclear facility to perform duties in such circumstances that there is a reasonable probability that the person may receive a dose of radiation that is greater than the prescribed limit for the general public (1 mSv/year). Every licensee shall use a licensed dosimetry service to measure and monitor the doses of radiation received and committed to nuclear energy workers who have a reasonable probability of receiving an effective dose greater than 5 mSv in a one year dosimetry period (Minister of Justice, 2000).

1 WLM = 5 mSv; the regulatory limit set for uranium workers in Canada is 100 mSv over 5 years, without exceeding 50 mSv per year (Minister of Justice, 2000). Cumulative annual dose is over a rolling 12 month period for exposed workers.

Occupation exposure to radon and its radon progeny is the product of <u>time</u> in the workplace and the <u>concentration</u> of radon progeny in the workplace air, measured in Working Level Months (WLM).

> **Working level (WL):** The concentration of radon progeny in workplace air is expressed in Working Levels (WL), where 1 WL is the concentration of radon progeny in one litre of air that will result in the emission of 1.3×10^5 MeV of potential alpha-particle energy after complete decay (ICRP 2010).
>
> **Working Level Month (WLM):** The cumulative exposure to an individual from breathing an atmosphere, at a concentration of 1 WL of radon progeny, over a time period of 1 working month of 170 working hours (ICRP 2010).

Radioactivity is measured in units called Becquerels (Bq). One Becquerel corresponds to the transformation (disintegration) of 1 atomic nucleus per second (WHO 2009, IAEA 2015, IAEA 2014).

Radon concentration is the activity of radon gas in terms of decays (i.e., transformations) per unit time in a volume of air. The unit of radioactivity concentration is given in Becquerel per cubic metre (Bq/m^3) (WHO 2009, IAEA 2015, IAEA 2014).

Uranium miner and **uranium worker** are used throughout this dissertation and refer synonymously to the underground uranium miners, open pit miners, mill workers or other mine workers who were included in any of the three country-specific cohorts.

Exposure, Concentration and Dose Units

- Joules (J): 1 J = 6.242×10^{12} MeV
- Working Level (WL):
  - 1 WL = 1.3×10^{8} MeV/m^3
  - 1 WL = 2.08×10^{-5} J/m^3
- Working Level Month (WLM):
  - 1 WLM = 3.54×10^{-3} J h/m^3
  - 1 WLM = 6.37×10^{5} Bq h/m^3 equilibrium equivalent concentration of radon
- The *exposure* unit for occupational radon and its radon progeny is the working level month (WLM).
- The *exposure* unit for long-lived alpha radionuclides is Becquerels per cubic meter per hour (Bq h/m^3).
- The *concentration* unit for residential radon is Becquerels per cubic meter (Bq/m^3)
- 1 Bq/m^3 of radon over 1 year = 4.4×10^{-3} WLM at home, assuming 7000 h/year indoors, and equilibrium factor (F = 0.4).
- 1 Bq/m^3 of radon over 1 year = 1.26×10^{-3} WLM at work, assuming 2000 h/year at work, and equilibrium factor (F = 0.4).
- The *dose* unit used for external gamma radiation is the millisievert (mSv).

(ICRP 2010)

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Abstract

Radon is a human carcinogen and is an important occupational and public health concern. Radiation protection programs, implemented since the 1950s and 1960s, have significantly reduced radon levels in uranium mines and improved the quality of exposure information. Precise quantification of the risk of lung cancer at low levels of radon exposure and the factors that confound and modify this risk are important for occupational radiation protection.

This is a joint cohort study of 408 lung cancer deaths and 394,236 person-years of risk from the Czech, French and Canadian male uranium miners, employed in 1953 or later, with cumulative radon exposures < 100 working level months (WLM). Internal Poisson regression models, stratified by cohort, age at risk and calendar year period at risk were used to calculate the linear excess relative risk (ERR) per unit cumulative radon exposure (lagged five-years). The impact of effect modifiers: time since exposure, attained age, and exposure rate were assessed using an exposure-age-concentration model. Finally, sensitivity analyses assessed the confounding effect of unmeasured tobacco smoking on the radon-lung cancer mortality risk estimate.

A statistically significant linear relationship between radon and lung cancer mortality was found, with ERR/WLM = 0.017 (95% confidence intervals (CI): 0.009–0.028) at < 100 WLM cumulative radon exposures. In trend analyses, statistically significant risk was observed at cumulative exposures as low as 10−19 WLM, with RR = 1.64 (95% CI: 1.03–2.65, N = 48 deaths). Radon exposures received in more recent periods (5–14 years previously) had the greatest risk of lung cancer mortality. These risks decreased with increasing time since exposure and attained age. No effect of exposure rate, separate from

measures of cumulative exposure, was observed at low radon levels. The confounding effect of unmeasured tobacco smoking was small and did not substantially change the radon-lung cancer mortality risk estimates found.

These findings provide strong evidence for an increased risk of lung cancer mortality after long-term low radon exposure among Czech, French and Canadian uranium miners. The results are compatible with other studies of miners restricted to low radon levels and residential radon studies. The results suggest radiation protection measures are of significant importance among modern uranium miners with low radon exposure levels.

Word Count: 366

1 Introduction

Radon and its radon progeny are classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC), meaning there is sufficient evidence of carcinogenicity in humans. The evidence comes largely from epidemiological studies of cancer in miners who started working underground before the 1950s and accumulated high radon exposures (i.e., a cumulative exposure > 500 WLM). Evidence also comes from studies of lung cancer associated with lower levels of cumulative exposure in homes, and from experimental studies of laboratory animals (IARC 2012c, IARC 2001, IARC 1988).

In the studies of miners, there were statistically significantly higher lung cancer rates than expected. Subsequent mine mechanical (forced air) ventilation systems, radiation monitoring, engineering techniques and other radiation protection measures led to a systematic drop in occupational radon levels to protect workers. Today, radon is strictly regulated in licensed uranium mines and processing facilities; radon concentrations are strictly controlled and must be monitored to protect workers (IRSN 2013, CNSC 2011, CNSC 2014).

In 1994, a joint analysis of 11 cohorts of radon-exposed miners was conducted. These cohorts included tin miners in Yunnan Province, China (Xuan, Lubin et al. 1993); iron ore miners in Malmberget, Sweden (Radford, Renard 1984); fluorspar miners in Newfoundland, Canada (Morrison, Semenciw et al. 1988). The joint analysis also included uranium miners from Australia (Radium Hill – (Woodward, Roder et al. 1991), Canada (Port Radium –(Howe, Nair et al. 1987); Beaverlodge – (Howe, Nair et al. 1986)

Ontario – Bancroft, Elliott Lake, Agnew areas – (Kusiak, Ritchie et al. 1993), Czechoslovakia (now the Czech Republic – (Tomasek, Darby et al. 1994, Sevc, Kunz et al. 1988)), France – (Tirmarche, Raphalen et al. 1993), and the USA (Colorado Plateau – (Hornung, Meinhardt 1987, Hornung, Deddens et al. 1995); New Mexico – (Samet, Pathak et al. 1991)). The joint analysis found a highly statistically significant linear exposure-response relationship between radon and lung cancer mortality (ERR/WLM = 0.0049; 95% CI: 0.002–0.010). Thus, the relative risk (RR) of lung cancer mortality at a cumulative radon exposure of 100 WLM was RR = 1.49. The radon-lung cancer mortality risk decreased with increasing time since exposure, attained age and exposure rate (or increasing duration of exposure). Most relevant to this dissertation, the exposure rate effect on the radon-lung cancer mortality relationship diminished at low exposures and low exposure rates.

Tobacco smoking was known to be an important risk factor for lung cancer and most miners smoked at higher levels than the general population. However, only six cohorts had individual level data on tobacco smoking so its potential confounding effect could not be well characterized. The joint effect of radon and tobacco smoking on lung cancer risk was between an additive and multiplicative effect (sub-multiplicative). However these analyses had only a small number of cases in several cohorts, which limited the statistical power (Lubin, Boice et al. 1994, National Research Council 1999, Lubin, Boice et al. 1995b, Lubin, Boice et al. 1995a, Lubin, Tomasek et al. 1997). Importantly, radon was not associated with a significant increase in risk for other cancers (Darby, Radford et al. 1995).

The extrapolation of lung cancer risk from high occupational radon exposures to low residential radon exposures was considered reasonable because of a limited number of case-control studies of residential radon at that time (National Research Council 1999, Lubin, Tomasek et al. 1997). This extrapolation was supported by a meta-analysis of eight case-control studies of residential radon (Lubin, Boice 1997). Large pooled analyses of residential radon case-control studies (Lubin, Wang et al. 2004, Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005, Darby, Hill et al. 2006, Darby, Hill et al. 2005) and a recent large cohort study using the American Cancer Society Cohort (Turner, Krewski et al. 2011) have found lung cancer risks at residential radon levels consistent with those extrapolated from studies of miners. However, important differences between occupational and residential radon and lung cancer risk make comparisons between these two populations difficult (i.e., predominantly male workforce, other occupational exposures, different breathing rates, shorter duration of exposure).

Since 1994, nine (9) out of the 11 cohorts in the joint analysis have been updated with extended mortality follow-up [Beaverlodge and Port Radium uranium miners (Lane, Frost et al. 2010), Newfoundland fluorspar miners (Villeneuve, Morrison et al. 2007), Ontario uranium miners (Navaranjan, Berriault et al. 2016); Colorado Plateau uranium miners (Schubauer-Berigan, Daniels et al. 2009), New Mexico uranium miners (Boice, Cohen et al. 2008), Czech uranium miners (Tomasek 2012), French uranium miners (Rage, Caer-Lorho et al. 2014), Swedish iron ore miners (Jonsson, Bergdahl et al. 2010)]. Also, the German Wismut uranium miner cohort was assembled and analyzed (Walsh, Grosche et al. 2015, Kreuzer, Grosche et al. 1999). However, most of these cohorts reflect the radon-lung cancer mortality relationship of miners with very high cumulative

radon exposures. Many miners worked prior to the implementation of radiation protection measures (especially mechanical (forced air) ventilation systems and routine monitoring of radon progeny) that drastically reduced the radon exposures of miners.

The International Commission on Radiological Protection (ICRP) reviewed recent epidemiological literature on the risk of lung cancer associated with exposure to radon progeny in underground mines (and in homes). A series of recommendations were made and a statement on radon was issued in the 2010 ICRP Publication 115 (ICRP 2010) that updated and revised the recommendations published previously in ICRP Publication 65 (ICRP 1993). An important conclusion of the ICRP Report 115 (ICRP 2010) was that the detriment-adjusted nominal risk coefficient for exposure to radon should be about twice the previous value assumed in ICRP Publication 65 (ICRP 1993). The ICRP recommendations on the risk of lung cancer at low annual exposure rates (ICRP 2010) were in line with those from other international committees (WHO 2009, United Nations 2009).

The ICRP is in the process of publishing dose coefficients per unit exposure to radon and its progeny for different reference conditions of occupational (and domestic) exposure. These revised dose coefficients will likely result in dose conversions coefficients that will be larger by a factor of approximately two or more, than the previous ICRP estimate of 6–20 mSv per WLM dose conversion coefficients (ICRP 1993). In the meantime, although current dose conversion coefficients may continue to be used, new and updated epidemiological studies of occupational (and residential) radon progeny exposure and lung cancer will provide objective scientific information to support ICRP's decision.

Today, uranium miners are exposed to very low occupational radon exposures that are comparable to levels people are exposed to in homes (CNSC 2014b, Health Canada 2012). Studies of miners with high and moderate radon exposures (pre-1950s) may not reflect the radon-lung cancer mortality risk of today's uranium miners. Studies of miners with low cumulative radon exposures, who worked when radiation protection measures were implemented (i.e., forced mechanical ventilation, routine monitoring of radon progeny), and who had measured rather than estimated radon exposures and extended mortality follow-up, better reflect the radon risks of today's uranium miners.

Potential confounding factors are especially relevant in today's miners since at low radon exposures the radon-lung cancer mortality relationship may be at the limit detectable by current epidemiological methods. Thus, any bias in the risk estimates due to confounding will have a greater impact on risk estimates at low radon exposure compared to the high radon exposures investigated in the past. Modifying effects also need to be accounted for in any statistical analysis; especially of the possible diminution of an exposure rate effect at low cumulative radon exposures (Lubin, Boice et al. 1995a, National Research Council 1999).

Therefore, the objective of the study was to combine updated data for the Czech, French and Beaverlodge uranium miner cohorts (Lane, Frost et al. 2010, Tomasek, Rogel et al. 2008, Rage, Caer-Lorho et al. 2014, Tomasek 2012) to enable analysis of a large sample size, with many more years of follow-up (~ 20,000 workers who in aggregate had ~ 450,000 person-years at risk, and ~ 650 lung cancers deaths). Most workers have had relatively low cumulative radon exposures at low exposure rates reflecting current occupational exposures. High-quality exposure measurement information was also

readily available. The analyses focused on the radon-lung cancer mortality relationship with careful consideration of the impact of potential confounding factors and the modifying effects of attained age, time since exposure and exposure rate.

2 Background

2.1 Uranium, Radon and Radon Progeny

Uranium-238 (^{238}U) is a ubiquitous naturally occurring radioactive element found in all soils and rocks (mainly igneous and metamorphic rocks) since the time the earth was formed. In some areas, uranium is concentrated in geological formations, making it feasible to extract it by conventional or other special mining methods. Triuranium octoxide (U_3O_8), a yellow powdery substance, is the most stable form of uranium oxide and is most commonly found in nature. Once uranium ore is mined, it is typically first processed at a nearby milling facility to recover this concentrate ("yellowcake"). The concentrate is then shipped to specialized processing and fabrication facilities that manufacture fuel for nuclear power reactors (CNSC 2014b).

Radon is an inert naturally occurring noble gas that has no taste, smell or colour (CNSC 2014b). It is produced mainly from the radioactive decay series of uranium, and thorium, in the earth's crust and is therefore present in soils, water and rocks. There are several isotopes of radon; the two most important are radon-222 (^{222}Rn), which is derived from uranium-238 (^{238}U), and radon-220 (^{220}Rn), which is derived from thorium-232 (^{232}Th). Radon-220, known as thoron, has a half-life of 54.5 seconds, whereas radon-222, known as radon, has a half-life of 3.83 days. Radon has 1.77×10^6 atoms per 100 pCi of activity, whereas thoron only has 260 atoms per 100 pCi of activity (Thompkins 1982). Therefore thoron contributes a negligible physiological effect on the body compared to radon, and will not be discussed further.

As illustrated in Figure 1 (the Uranium-238 decay series), uranium (^{238}U) has a half-life of 4.5 billion years, has 13 radioactive products and involves 8 alpha particle and 6 beta

particle transitions before one uranium atom (^{238}U) becomes a non-radioactive stable atom of lead (^{206} Pb). Radium (^{226}Ra), which is just before radon on the decay chain, has a 1,590 year half-life so is an infinite source of radon gas (^{222}Rn) (Thompkins 1982).

Radon is a radioactive alpha (α) particle emitter that spontaneously decays, or changes to other atoms very quickly. It has a short half-life of 3.83 days. As a gas, radon can migrate freely through the microscopic pores of the rock, fissures within the mineral formation or the open working spaces of the mine before completely decaying to ^{218}Po (Thompkins 1982).

Radon decays into four very short-lived radioactive isotopes. These are termed radon progeny, radon decay products, or radon daughters and consist of solid, electrically-charged particles of three elements: polonium-218 (^{218}Po), lead-214 (^{214}Pb), bismuth-214 (^{214}Bi), and polonium-214 (^{214}Po) (National Research Council 1999). Like radon gas, radon progeny can also be suspended in air and can attach to dust particles. Both attached and unattached fractions can be inhaled and may then embed in the lungs and other parts of the respiratory system. Because of their relatively short half-lives (less than half an hour), the radon progeny mainly decay in the lung, before clearance can take place.

Two very short-lived progeny, polonium-218 (half-life = 3.05 minutes) and polonium-214 (half-life = 1.5×10^{-4} seconds), which emit alpha particles, give the bulk of the dose from radon to the epithelial cells lining the respiratory tract and the lungs. The energy from these two radon progeny are recognized as the primary sources of the ionizing energy delivered to the respiratory epithelium of the lungs, associated with the

development of lung cancer (CNSC 2014a, ICRP 2007, National Research Council 1991, CNSC 2011).

Radon's alpha particles produce a wide variety of molecular damage in the cell. *In vitro* and *in vivo* experimental studies have documented biological effects of alpha particles, including DNA double-strand breaks, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations, gene mutations, and cell transformation (IARC 2012c, IARC 2001, IARC 1988).

The term radon is used throughout this dissertation to refer to radon-222 and its short-lived radioactive decay products (radon progeny, radon daughters) synonymously.

2.1.1 Types of radiation and dose concepts

Ionizing radiation is constantly present in the environment and is emitted by natural and artificial sources (CNSC 2011a). There are four main types of ionizing radiation:

- alpha (α)
- beta (β)
- photon (X-rays and gamma (γ) rays), and
- neutrons

Beta-particles (although part of the uranium-238 decay chain), X-rays and neutrons are not directly relevant to this study; however, a basic understanding of the different types of radiation and dose concepts, will help when reading this dissertation.

Alpha and beta particles may be emitted when a nucleus undergoes radioactive decay. This is often also accompanied by the release of additional energy in the form of photon

radiation, certain forms of energetic electromagnetic radiation. Two types of photon radiation are important for dosimetry: gamma (γ) and X-ray. Neutron radiation can only be produced from nuclear fission, which occurs for certain nuclear substances with a high atomic number, such as uranium and plutonium (CNSC 2011a).

Regardless of the source, each of these radiation types is capable of penetrating the human body to a varying degree and delivering a radiation dose. Alpha radiation (α) consists of alpha particles that consist of two protons and two neutrons each and that carry a double positive charge. Due to their large mass and charge, alpha particles are unable to penetrate into the skin, so do not pose an external radiation hazard. However, when alpha-radiation-emitting nuclear substances are internalized (e.g., by inhalation, ingestion), its energy is nearly completely absorbed in tissues such as the lungs (CNSC 2011a). Hence, radionuclides emitting alpha radiation (Rn-222) are an important internal radiation hazard with potentially large resulting doses (ICRP 2010). Beta (β) particles can penetrate the outer layers of the skin, and are also hazardous if taken into the body. Photon radiation (gamma (γ) radiation, X-rays) and neutrons can penetrate into and through tissues and organs, resulting in different levels of damage depending on their energy level. Hence they pose both an external and an internal hazard (CNSC 2011a)

When ionizing radiation penetrates the body, it deposits energy. The energy absorbed per unit mass from exposure to radiation is called a dose. There are three fundamental dose quantities in practical radiation protection for humans (CNSC 2011a):

- absorbed dose
- equivalent dose and
- effective dose

The absorbed dose is the amount of radiation energy absorbed per unit mass in a substance (i.e., human tissue). It is measured in gray (Gy). The equivalent dose is the absorbed dose, weighted for the relative biological effectiveness of *different radiations*. It is measured in sieverts (Sv). Finally, effective dose is the equivalent dose, weighted for the sensitivities of *different tissues*. It is also measured in Sv. One sievert (1 Sv) is equivalent to 1,000 millisieverts (mSv) (CNSC 2011a).

2.1.2 Internal dosimetry

Since radon and its short-lived radon progeny are internal sources of radiation. Internal dosimetry is used in the measurement of doses due to radon and its radon progeny that have entered the body by way of inhalation, ingestion or other means. Internal dosimetry for radon progeny involves two steps; first, the level of radiation inside the body is estimated using the measurement of radioactivity in workplace air, and second, the resulting internal radiation dose is calculated (CNSC 2011a).

Short-lived radon progeny have such short half-lives they decay quickly before their activity could be measured via bioassay methods. Radiation from radon progeny must therefore be measured in workplace air. There are both indirect monitoring and direct monitoring methods (CNSC 2011a).

Indirect monitoring methods use measured airborne concentrations of nuclear substances. This method is used when a worker, or group of workers, occupy an area with a known concentration of airborne radioactivity, for a known period of time. This information in conjunction with other information is used to estimate the worker's radiation dose during the particular occupancy. In such situations, the concentration in air of radon progeny is

measured by air sampling, and the time spent in the area by a worker is recorded. Measurements such as concentrations of airborne radioactivity, recorded period of occupancy and air inhalation rates can then be used to estimate the individual's dose. This method is referred to as workplace monitoring (CNSC 2011a).

For workers most likely to be exposed, a personal alpha dosimeter (PAD) is used to estimate individual exposures to radon progeny. A PAD consists of a battery-operated pump and a filter. Air is drawn through the dosimeter and the filter captures the radon progeny. As they decay, they emit alpha particles which interact with a cellulose film placed a few centimeters from the filter. These interactions cause damage (tracks) to the cellulose film. The numbers of tracks are counted using a microscope and a calibration factor converts the number of tracks into an air concentration of radon progeny. The worker's exposure is calculated by taking the concentration of radon progeny in air and the exposure time into account (CNSC 2011a).

In Canada, exposure results are reported to the National Dose Registry and are expressed in a unit of exposure called the working level month (WLM). It is more practical to measure occupational exposure to radon and its radon progeny than dose (WHO 2009, IAEA 2015, IAEA 2014). This is because the health risk from radon is related to the concentration of the alpha-particle energy released by its radon progeny in air. Instead of determining the concentration of each radon progeny in air, it is simpler to measure the concentration of alpha-particle energy released by all radon progeny in air. This quantity is called the potential alpha energy concentration (PAEC), which is the amount of alpha-particle energy per unit volume of air that can be released from the radon progeny.

The PAEC unit is known as the working level (WL), where 1 WL is the concentration of radon progeny (^{218}Po, ^{214}Pb, ^{214}Bi, ^{214}Po) in one litre of air that will result in the emission of 1.3 x 10^5 MeV of potential alpha-particle energy after complete decay (ICRP 2010). Exposure to radon progeny is determined by the PAEC multiplied by the amount of time a person is exposed to radon progeny. Thus, accurate records of time spent by workers in the workplace are necessary. Exposure is usually expressed in working level months (WLMs), with a working month being defined as 170 hours. Thus, if a person is exposed to 1 WL of radon progeny over a full working month of 170 hours, then the exposure would be equal to 1 WLM. The WLM value is related to dose on the basis of epidemiological studies. Currently, 1 WLM equals a dose of 5 mSv (ICRP 1993) and this value is identified in the radiation protection regulations of most countries.

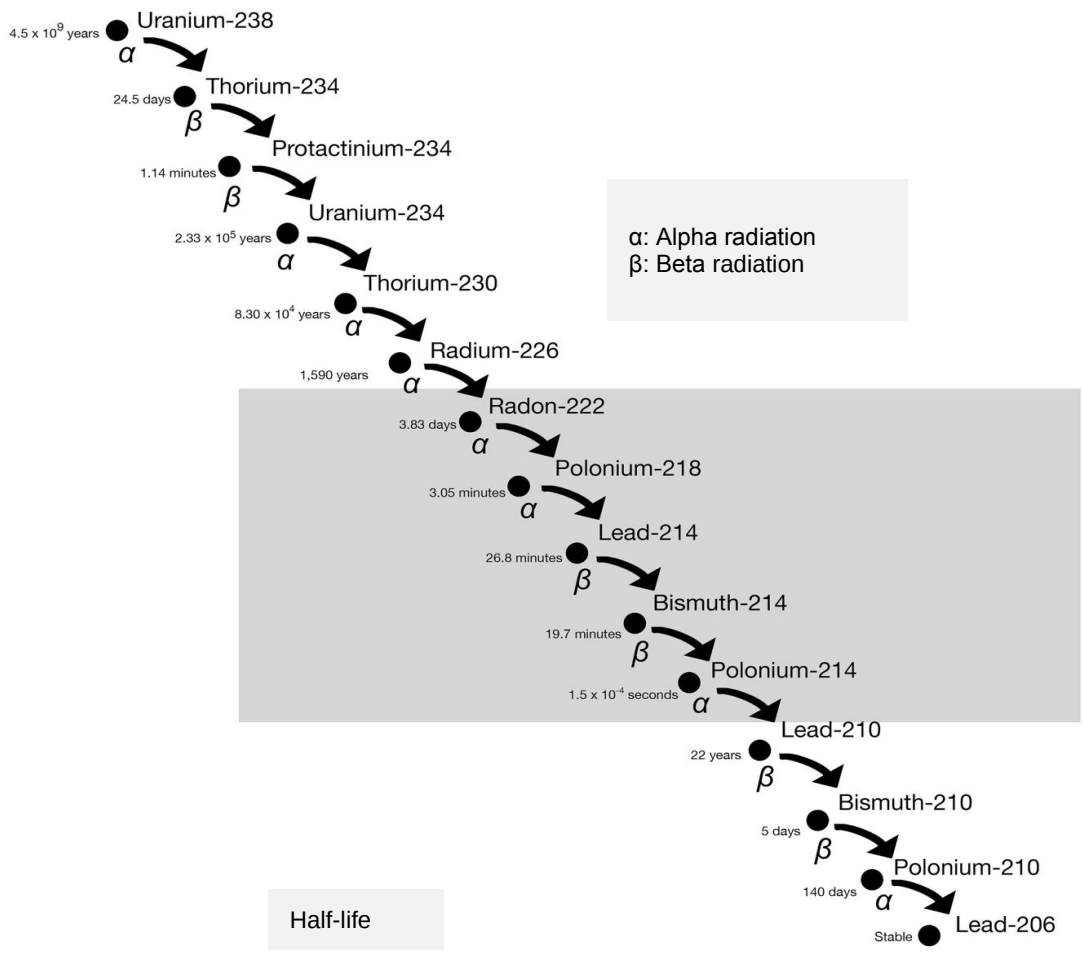

Figure 1 Uranium-238 decay chain

Figure adapted from BEIR VI report (National Research Council 1999). The large grey shaded area highlights the fast decay of radon and its radon progeny.

2.2 Early Studies of Radon-Exposed Miners

Mining has been carried out in the Erz Mountains on the border between Czechoslovakia and Germany, for several centuries. Mining began in the 15th century with the mining of metal ores in southern East Germany, and in the 16th century in nearby mines of Joachimsthal in West Bohemia (then part of Czechoslovakia, now part of the Czech Republic) (Tomasek, Swerdlow et al. 1994, Sevc, Tomasek et al. 1993, Sevc, Kunz et al. 1988).

As early as the 16th century Agricola described exceptionally high mortality from pulmonary disease (Bergsucht) in miners in this area (Hoover, Hoover 1950, Langard 2015). This disease was recognized as cancer in 1879 among Schneeberg miners, on the German side, when autopsy findings documented pulmonary malignancy (Harting, Hesse 1879). By the early 20th century the malignancy was shown to be primary carcinoma of the lung (Arnstein 1913). High lung cancer rates in both areas led to the suggestion that radon was the cause (Ludwig, Lorenser 1924, Pirchan, Sikl 1932, Jacobi 1994, Proctor 1995, Lorenz 1944).

Subsequently, Harley postulated that the short-lived radon progeny of radon were the source of the largest doses of ionizing radiation to lung cells (Bale 1980, Harley 1981, Harley 1952, Harley 1953, Harley 1980). The bulk of the dose from radon is derived from two very short-lived daughters, polonium-218 (half-life = 3.05 minutes) and polonium-214 (half-life = 1.5×10^{-4} seconds). These daughters are now recognized as the primary sources of the ionizing energy delivered to the respiratory epithelium of the lung by radon (National Research Council 1991).

2.3 Uranium Mining in the Czech Republic, France and Canada

Uranium mining in Czechoslovakia (now the Czech Republic) began in 1946 at the Jáchymov mines, producing uranium for the Soviet Union. Early mining sites included Jáchymov, Horní Slavkov and Příbram. The largest deposit, Příbram, produced about 50,000 tonnes of uranium (tU) and was mined to a depth of over 1,800 m. Czech uranium mining, which once provided over 2500 tU per year, declined rapidly from 1990 following the collapse of the Communist government. A total of 110,427 tU was produced from 1946−2008, from 64 uranium deposits. However, by 1994 Czech production had fallen to 600 tU per year, and in the last decade production declined steadily to 155 tU per year in 2015. The last underground mine (Rožná deposit) is scheduled to close in 2017 (World Nuclear Association 2016).

In France, uranium was mined in about 250 sites across the country from 1948 (Henriette mine) to 2001 (Jouac mine), with production totalling nearly 80,000 tons. Uranium mining ended in France in 2001 (World Nuclear Association 2016).

In Canada, uranium mining began in 1942 in the Northwest Territories (Port Radium), primarily for military research purposes at that time. Other mines began production in the early 1950's with the discovery of major deposits in northern Saskatchewan (Beaverlodge, Lorado, Gunnar mine sites) and Ontario (Elliott Lake, Bancroft, Agnew areas). A second phase of exploration in the 1970s resulted in major discoveries in the Athabasca Basin in northern Saskatchewan. Mines at Rabbit Lake, Cluff Lake and Key Lake started up in 1975, 1980, and 1983, respectively. A third phase of exploration resulted in the start-up of development of the Cigar Lake mine in 1990, the McArthur

River mine in 1997, and the McLean Lake mill in 1994 (CNSC 2014b). Uranium mines employed a predominantly male workforce; over 90% of current uranium miners are male (Health Canada 2008).

The initial Canadian uranium mines have been decommissioned. Today, all operating uranium mines and mills in Canada are in northern Saskatchewan (McArthur River mine, Key Lake mill, Cigar Lake mine, Rabbit Lake mine and mill, McClean Lake mill). Uranium production comes mainly from the McArthur River mine and the new Cigar Lake mine that began production in 1999 and 2014, respectively (CNSC 2014b). These two mine sites have the world's two largest high-grade uranium ore deposits. With known uranium resources of 485,000 tU, as well as continuing exploration, Canada has a significant role in meeting future world demand for uranium. This is expected to continue to rise for the foreseeable future. Ninety percent (90%) of Canada's uranium is exported (World Nuclear Association 2016, NEA-OECD 2014).

2.4 Joint Analysis of 11 Cohorts of Radon-Exposed Miners

After World War II and the escalation of mining of uranium for military purposes, new epidemiological studies were initiated to determine the safety of exposures to radon progeny (Proctor 1995, National Research Council 1988).

The most definitive analysis reported to date for estimating radon-associated lung cancer risk is the pooling of original data from 11 cohort studies of male, underground miners. Cohorts where selected using objective inclusion criteria established *a priori*: A minimum of 40 lung cancer deaths and estimates of radon progeny exposure in units of WLM for each member of the cohort. These were based on historical measurement of either radon gas or radon progeny. The first criterion was meant to avoid the difficulties of handling multiple small data sets. The 11 cohort studies were thought to include all published studies that meet these criteria. These studies represented more than 2,700 lung cancer deaths among over 65,000 miners who accumulated over nearly 1.2 million person-years of observation (Lubin, Boice et al. 1994, Lubin, Boice et al. 1995b).

The constant linear excess relative risk model was fitted for each cohort. The study-specific excess relative risk per unit of working level month (ERR/WLM) estimates ranged from 0.002 (China) to 0.051 (Radium Hill). This corresponded to RRs at 100 WLM ranging from 1.2 to 6.1, which was a wide range across the cohorts. However, except for Radium Hill, most estimates of ERR/WLM were about 0.02 or less (RR at cumulative radon exposure of 100 WLM = 3.0 or less), but differed by about 10-fold in magnitude. The overall ERR/WLM was 0.0049 (95% CI: 0.002–0.010) or a RR at a cumulative radon exposure of 100 WLM = 1.49.

The relative risk of lung cancer for cumulative radon progeny exposures was found to be a highly statistically significant linear relationship over a wide range (up to 3,200 WLM) of cumulative exposures. Overall, there was no significant departure from linearity, in particular, when exposures were limited to less than 400 WLM. This suggested that exposures at lower levels would carry some risk (Lubin, Boice et al. 1994).

When the joint cohort was restricted to < 50 WLM or < 100 WLM cumulative radon exposures, the RRs for categories of WLM exhibited a statistically significant increasing trend with exposure in each of the restricted data sets (Lubin, Tomasek et al. 1997). The excess relative risks for the < 50 WLM and the < 100 WLM data restrictions were ERR/WLM = 0.012 (95%CI: 0.002–0.025) and ERR/WLM = 0.008 (95%CI: 0.003–0.014), respectively (Lubin, Tomasek et al. 1997).

2.4.1 Effect modifiers in the 11-cohort analysis

Lubin and colleagues (Lubin, Boice et al. 1995b, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1994, Lubin, Tomasek et al. 1997) also observed the radon-lung cancer mortality relationship was modified by temporal variation in the effects of past radon exposure (i.e., cumulative exposures in different windows of time since exposure ceased, exposure rate, duration of exposure) and characteristics of workers (i.e., attained age, age at first exposure). The ERR/WLM decreased with increasing attained age and time since exposure but was not related to age at first exposure. However, limited mortality data were available for young miners. Only the Chinese cohort had lung cancer cases among miners first exposed before 15 years of age, since very few workers were exposed in this age group. Nine cohorts had lung cancer cases among miners first exposed when they were 15−24 years of age (Lubin, Boice et al. 1994).

Over a broad range of total cumulative exposures, higher lung cancer risk was associated with radon exposures received at low exposure rates (or over long durations) than with exposures received at high exposure rates (or short durations). Thus for the same total exposure, exposures received at high exposure rates were less harmful that those received at lower exposure rates, known as an "inverse exposure rate" effect. However, a diminution of the "inverse exposure rate" effect for low cumulative radon exposures was observed. Below 50 WLM a decrease was not apparent, particularly at lower exposure rates (less than about 0.5 WL) although analyses were necessarily hampered by a limited range of exposure rates at low cumulative exposures which could result in a lack of statistical power to detect such a diminution of effect (Lubin, Boice et al. 1995b). However, the diminution of the inverse exposure rate effect at low cumulative exposures was consistent with bio-physiological models (Brenner 1994, Brenner, Hall 1990, Brenner, Hall et al. 1993), experimental animal studies (Collier, Strong et al. 2005, Morlier, Morin et al. 1992) and *in vitro* studies (Miller, Randers-Pehrson et al. 1993) at that time.

2.4.2 Other risk factors in the 11-cohort analysis

2.4.2.1 Tobacco smoking in subset of six cohorts

Underground miners were known to be heavy smokers. However; individual level data on tobacco smoking was either lacking entirely, not readily comparable across cohorts, or incomplete for workers within the cohort (Lubin, Boice et al. 1994). Six cohorts (Chinese tin miners, Swedish iron ore miners, Newfoundland fluorspar miners, and the Colorado Plateau, New Mexico, and Radium Hill uranium miners) had partial data on smoking status or smoking practices, but a substantial number of workers lacked smoking

information (Xuan, Lubin et al. 1993, Samet, Pathak et al. 1991, Morrison, Semenciw et al. 1988, Hornung, Meinhardt 1987, Radford, Renard 1984, Woodward, Roder et al. 1991). Smoking surveys were not undertaken on a regular prospective basis so Lubin and colleagues (1994) had to assume the smoking practices were constant in time. Finally smoking may have been underreported by workers concerned about health compensation. Because of the many uncertainties in the smoking data within each cohort and the lack of comparability among the cohorts, the smoking data were only presented for individual cohorts.

The analyses of smoking data for each cohort found no clear pattern of risk for the joint association of smoking and radon exposure (Lubin, Boice et al. 1994). The joint effects of radon and tobacco smoking on lung cancer mortality risk were assessed using several statistical approaches. The most consistent model for the six cohorts was intermediate between an additive and multiplicative interaction (i.e. sub-multiplicative). However, analyses were limited by incomplete data on tobacco use and inadequate data to characterize lifetime smoking patterns.

A joint analysis was also conducted of the subgroup of workers who were never-smokers. The excess relative risks of lung cancer increased with cumulative radon exposure for both ever-smokers and never-smokers. Among the cohorts with smoking information, 50,493 person-years and 64 lung cancer deaths occurred among workers who had never smoked. A linear exposure-response trend was observed which was about three-fold higher in never-smokers (ERR/WLM = 0.0103; 95% CI: 0.002–0.057) compared to ever-smokers (ERR/WLM = 0.0034; 95% CI: 0.001–0.015). However, the extremely wide confidence intervals made these findings difficult to interpret (Lubin, Boice et al. 1994).

2.4.2.2 Other occupational exposures in subset of five cohorts

Finally, five cohorts had very limited individual level data on arsenic exposure or prior mining experience other than radon (Colorado, New Mexico, French, and Ontario uranium miners, Chinese tin miners). Exposure to arsenic increased the risk of lung cancer, while adjustments for arsenic exposure reduced the estimated ERR/WLM. After adjusting the risk of lung cancer for arsenic exposure, the ERR/WLM did not vary significantly within categories of arsenic exposure. Similarly, adjustment for previous mining experience lowered the ERR/WLM estimates only slightly (Lubin, Boice et al. 1994).

2.4.3 Main conclusions of the 11-cohort analysis

The main conclusion of the joint analysis of 11 cohorts of radon-exposed miners was that the risk of lung cancer mortality increased linearly with cumulative radon exposure. The modifying effects of the radon-lung cancer mortality relationship included the time since exposure, attained age, exposure rate, and duration of exposure. Risk decreased with increasing time since exposure windows, increasing attained age, and either increasing exposure rate or decreasing duration of exposure. Also, an inverse exposure rate effect diminished at low cumulative radon exposures, consistent with biological models (Lubin, Boice et al. 1994). Finally, a joint effect of tobacco smoking and radon was observed somewhere between an additive and multiplicative interaction (sub-multiplicative).

In 1999, the National Research Council's Sixth Committee on the Biological Effects of Ionizing Radiation (BEIR VI) adopted the work of Lubin and colleagues (Lubin, Boice et al. 1995b, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1994, Darby, Whitley et al. 1995, Lubin, Tomasek et al. 1997) and recommended two risk models for a linear relationship

in the excess relative risk of lung cancer for cumulative radon exposures. In both, the exposure-response was modified by temporal variation in the effects of past exposure (time since exposure windows), current age (attained age) and either exposure rate or exposure duration. These two risk models were referred to as the exposure-age-concentration model and the exposure-age-duration model (National Research Council 1999).

2.4.4 Main limitations of the 11-cohort analysis

Although the joint analysis of 11 miners is a seminal body of work, several considerations suggest that its findings are not generalizable to modern uranium miners (Lubin, Boice et al. 1995b, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1994, Lubin, Tomasek et al. 1997).

First, there was substantial measurement error of radon exposures. This was especially common in the early time periods when miners' exposure estimates were often based on very limited information, such as a few mine wide 'estimates' made years after the fact. Second, several cohorts included miners with extremely high cumulative radon exposures (> 500 WLM), which do not reflect current occupational exposures. Third, although the quality of measurements for low cumulative radon exposures improved substantially after the implementation of radiation protection programs, the mortality follow-up of these workers was not sufficient. Fourth, there was inadequate information on potential confounding factors; especially tobacco smoking and other occupational carcinogens (i.e., gamma radiation, long lived radionuclides, arsenic, silica, diesel exhaust) in the mine environment. Finally, several of the cohorts had very diverse populations (i.e. children, conscripted volunteers, prisoners of war) which limit their generalizability to current

uranium miners (Lubin, Boice et al. 1995b, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1994, Lubin, Tomasek et al. 1997).

2.4.5 Cancers other than lung cancer, and other causes of death

In 1995, Darby and colleagues assessed the risk of radon and its progeny on cancers other than lung cancer, using 11 cohorts of underground miners in which radon-related excesses of lung cancer had been investigated (Darby, Whitley et al. 1995). This included ten of the 11 cohorts from the earlier joint analysis (Lubin, Boice et al. 1994). The Radium Hill study (Woodward, Roder et al. 1991) was excluded since follow-up was incomplete and the Cornwall tin miners study (Hodgson, Jones 1990) was added.

This study provided strong evidence that high radon concentrations in air do not increase the risk of death from cancers other than lung cancer. For all non-lung cancers combined, an external analysis found that mortality was close to that expected from mortality rates in the areas surrounding the mines (Observed/Expected = 1.01; 95% CI: 0.95–1.07, 1179 deaths) and there was no evidence of a trend with cumulative exposure when considering all years (ERR/WLM = 0.0002; 95% CI: -0.0001–0.0003) or 10 or more years since first employment (ERR/WLM = 0.0001; 95% CI: -0.0001–0.0002).

Of 28 individual cancer sites studied, statistically significant excess mortality was only found for cancers of the stomach (O/E = 1.33; 95% CI: 1.16–1.52) and liver (O/E = 1.73; 95% CI: 1.29–2.28). Leukemia mortality was only increased in the period less than 10 years since starting work (O/E = 1.93; 95% CI: 1.19–2.95). However, no significant relationship between mortality from these cancer sites (stomach, liver, leukemia) and cumulative exposure was found, so they are unlikely to be caused by radon. Only deaths

due to pancreatic cancer (ERR/WLM = 0.0007; 95% CI: 0.0001–0.0012) and, ‘other and unspecified cancer’ (ERR/WLM = 0.0022; 95% CI: 0.0008–0.0037) were related to cumulative radon exposure; however, risk estimates were very low and seem likely to be chance findings (Darby, Whitley et al. 1995).

2.5 Updated Studies of Radon-Exposed Miners

To date, a statistically significant linear relationship between occupational radon exposure and increased lung cancer risk has been found in 19 cohorts of underground miners exposed to radon. These studies have provided our best quantitative estimates of radon risks to miners. The International Commission on Radiological Protection (ICRP) used this scientific evidence as the basis for its recommendation to establish national reference levels (i.e. radon exposure limits) as an aid to optimisation of protection against radon (ICRP 1993). Active radiation protection measures, especially systematic mechanical (forced air) ventilation systems, have substantially reduced occupational radon exposures. Modern regulations similarly include requirements for monitoring of radiation/radon exposures. Consequently, the number and quality of radon exposure estimates has increased substantially and individual exposure measurements are now readily available. This has substantially improved the quality of exposure data for epidemiological studies (IARC 2012c, IARC 1988, IARC 2001).

Since 2007, nine cohort studies have extended their mortality follow-up (Beaverlodge, Port Radium, Ontario, Czech Republic, Colorado Plateau, New Mexico and French uranium miners, the Newfoundland fluorspar miners, and the Swedish iron miners) (Lane, Frost et al. 2010, Tomasek 2012, Schubauer-Berigan, Daniels et al. 2009, Villeneuve, Morrison et al. 2007, Jonsson, Bergdahl et al. 2010, Boice, Cohen et al. 2008, Rage, Caer-Lorho et al. 2014, Navaranjan, Berriault et al. 2016) and the German cohort of Wismut uranium mines has been extensively analyzed (Walsh, Tschense et al. 2010).

These ten updated cohort studies (nine of which were included in the original joint analysis – Chinese tin miners and Australian Radium Hill uranium miners have not been

updated), support the risk model of the joint analysis of 11 cohorts of radon exposed miners (National Research Council 1999, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1995b), giving increased statistical power and precision. Many of these updates also substantially improved the quality of identifying information important for record linkages and exposure information (including individual measurements) and extended mortality (and in some cases cancer incidence) follow-up. The cohorts are also 20−30 years older, so more miners are of the age when cancer and chronic disease rates are high. The potential impacts of tobacco smoking, gamma radiation, and long-lived radionuclides in dust, arsenic, and silica have been assessed in some cohorts. Likewise, the impacts of different effect modifiers on the radon-lung cancer mortality relationship have been assessed.

Table 2-1 provides results from cohorts of underground miners which include those from joint cohort analyses and those focused on relatively low cumulative radon exposures or time periods of quality radon measurements. These results are particularly important since they provide consistent estimates of lung cancer risk and show statistically significant associations at cumulative occupational radon exposures of about 50 WLM (ICRP 2010, Tomasek, Rogel et al. 2008, Hunter, Muirhead et al. 2013, Kreuzer, Fenske et al. 2015, Lubin, Tomasek et al. 1997, United Nations 2009, National Research Council 1999, Rage, Caer-Lorho et al. 2014, Lane, Frost et al. 2010, Leuraud, Schnelzer et al. 2011).

The European Commission's Alpha-Risk Project has also conducted substantial analysis of a joint nested case-control study within the three European cohorts (Czech, French, and German-Wismut) of uranium miners (1046 cases/2492 controls) (Leuraud, Schnelzer

et al. 2011, Hunter, Muirhead et al. 2013). A linear excess of lung cancer risk with cumulative radon exposure was found. Refinement of the relationship between lung cancer risk and radon exposure, considering only periods with good quality exposure data and low exposure rates, found that lung cancer risk coefficients were very consistent between the three cohorts. Analyses also confirmed the importance of modifying factors for the exposure-risk relationship, particularly the effects of time since exposure. In the unrestricted sample, the ERR/WLM = 0.010 (95% CI: 0.006–0.018). The ERR/WLM = 0.008 (95% CI: 0.004–0.014) when adjusted for smoking. When the data was restricted to cumulative exposures < 300 WLM and adjusted for smoking status, the ERR/WLM = 0.0174 (95% CI: 0.009–0.035), compared to an ERR/WLM = 0.023 (95% CI: 0.012–0.042) [Dr. Nezahat Hunter, personal communication, 2016-10-17]. The results confirmed that the lung cancer effect of radon was not greatly impacted by tobacco smoking and persisted even when smoking was adjusted for, with arguments in favor of a sub-multiplicative interaction between radon and smoking. The ERR/WLM was greater for non-smokers compared with current or ex-smokers, although there was no statistically significant variation in the ERR/WLM by smoking status. The patterns of risk with radon exposure from the joint European nested case-control miner analysis were generally consistent with those of the BEIR VI exposure-age-concentration model (Tirmarche, Laurier et al. 2010, Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013).

Table 2-1 Summary of lung cancer mortality (ERR/WLM) by cumulative radon exposure at low exposures or exposure rates from published studies of miners

Reference	No. of cohorts	Included	No. of miners or (cases, controls)	Person-years	ERR/WLM	SE	95% CI
(Lubin, Boice et al. 1994)	11	All	60,570	908,903	0.0049		0.002–0.010
(United Nations 2009)	9	All	125,627	3,115,975	0.0059		0.0035–0.010
(National Research Council 1999)	11	All	60,705	892,547	0.0059	1.32	
(Lubin, Tomášek et al. 1997)	11	All					
		< 100 WLM	562	564,772	0.008		0.003–0.014
		< 50 WLM	353	453,604	0.012		0.002–0.025
(Tomášek, Rogel et al. 2008) measured exposures, Cz 1952–95, Fr 1946–94	2	All	10,100	248,782	0.027		0.017–0.043
(Lane et al. 2010) BL 1948–99	1	All	9,498	285,964	0.0096		0.0056-0.016
(Hunter, Muirhead et al. 2013) Cz 1948–99, Fr 1946–94 & Gr 1946–98	3	All	(1046 cases, 2492 controls)		0.008		0.004–0.014
		< 300 WLM	(742 cases, 2088 controls)		0.017		0.009–0.035
(Rage, Caer-Lorho et al. 2014) Fr 1956–07	1	All	3,377	110,548	0.024		0.009–0.051
(Kreuzer, Fenske et al. 2015) Gr 1960–08	1	All	26,766	846,809	0.013		0.007–0.021
		< 100 WLM			0.016		0.008–0.028
		< 50 WLM			0.013		0.001–0.029
(Navaranjan, Berriault et al. 2016) Ont. 1954–07	1	> 100 WLM	28,546		0.064		0.043–0.085

SE, standard error; CI confidence interval. Adapted from ICRP 2011 Proceedings (Tirmarche, Harrison et al. 2012).
Shaded areas represent either recent studies restricted to low cumulative exposures, or time periods when mechanical ventilation, routine radon monitoring and high quality exposure measurements were in place.

A linear exposure-response relationship was found in the updated Beaverlodge, French and Czech cohorts of uranium miners and a joint analysis of the French and Czech cohorts. There was little evidence to suggest any departure from linearity, other than that which might be due to statistical fluctuations. Likewise, the linear trend with overall cumulative exposure fit the relative risk well at exposures below about 200 WLM (in the joint French and Czech cohort study) and < 7 WL exposure rate (in the updated Czech study) (Lane, Frost et al. 2010, Tomasek, Rogel et al. 2008, Rage, Caer-Lorho et al. 2014, Tomasek 2012).

These findings are consistent with many other studies assessing the relationship between cumulative radon exposure and lung cancer mortality. This includes updated studies of miners and large joint residential radon case-control studies with high quality radon measurements, low radon exposures and exposure rates, and detailed consideration of potential confounding by tobacco smoking (Kreuzer, Fenske et al. 2015, National Research Council 1999, United Nations 2009, Tomasek, Rogel et al. 2008, Hunter, Muirhead et al. 2013, Rage, Caer-Lorho et al. 2014). Although other non-linear models (such as quadratic, linear-quadratic or log-linear) have been assessed at low cumulative exposures, they did not improve significantly the model fit (Kreuzer, Fenske et al. 2015).

Some biological effects following exposure to alpha-particles, such as the bystander effect, have been observed in cells and in other experimental systems, and imply that linearly extrapolating low-dose risks from high-dose data may underestimate risk. However, even if these biological effects apply to human cells *in vivo*, the accumulated epidemiological data suggest that these biological effects do not play a large part in the

process of radon-induced lung carcinogenesis in humans. Thus, risk assessments have concluded that the risk of developing lung cancer increases linearly as the exposure increases, i.e. that the increase in risk is linear) is appropriate (National Research Council 1999, Brenner, Sachs 2003, Little 2010, Little, Wakeford 2002, Kadhim, Salomaa et al. 2013, Little 2004).

2.5.1 Effect modifiers

Updates of existing cohorts of radon-exposed miners (Villeneuve, Morrison et al. 2007, Lane, Frost et al. 2010, Tomasek 2012, Vacquier, Rogel et al. 2009), the German (Wismut) cohort of uranium miners (Walsh, Tschense et al. 2010, Walsh, Dufey et al. 2010, Walsh, Grosche et al. 2015), joint analyses of the European cohorts (Tomasek, Rogel et al. 2008) and joint nested case-control studies of uranium miners (Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011) have expanded the understanding of effect modifiers on the radon-lung cancer mortality relationship. These studies assessed the modifying effects of several variables on the radon and lung cancer relationship, including time since exposure, age at exposure, attained age, quality of exposure estimates (estimated, measured), exposure rate, period of exposure, physical activity level, duration of exposure, job type, mine type, and smoking status.

Quality of exposure estimates was an important factor that substantially influenced results. The risk of lung cancer was greater among “measured” exposures, which reflected increased accuracy of measured exposures compared to the uncertainty in “estimated” exposures in the French and Czech uranium miners (Tomasek, Rogel et al. 2008). However, the quality of exposure estimates did not substantially influence results in the German uranium miners (Kreuzer, Schnelzer et al. 2010, Grosche, Kreuzer et al.

2006). Likewise, the period of exposures was an important modifier in the French cohort (Vacquier, Rogel et al. 2009) and a French, Czech and German nested case-control study (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2015). The ERR/WLM was higher for exposures received in time periods of mechanical ventilation and routine radon progeny measurements (high quality exposure measurements), compared to earlier time periods. However, time period was not an effect modifier in the Newfoundland fluorspar miners (Villeneuve, Morrison et al. 2007). The physical activity level of the job significantly modified the exposure-risk relationship in French miners. The ERR/WLM was higher for 'hard physical activity'. A significant modifying effect of mine type was also observed. Underground miners had higher ERR/WLMs than open pit miners (Vacquier, Rogel et al. 2009).

Time since exposure was the most important effect modifier. It had the greatest modifying effect on the radon-lung cancer relationship, compared to other effect modifiers (Tomasek, Rogel et al. 2008, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Lane, Frost et al. 2010, Tomasek 2012). For the same cumulative exposure, the ERR/WLM of exposures received in the most recent past (i.e., 15–24 years since attained age) was significantly greater than exposures received in the most distant past (i.e., 25+ years since attained age). However, the ERR/WLM did not differ by time since median exposure in German miners restricted to the period after 1960 for miners exposed to < 100 WLM (Kreuzer, Fenske et al. 2015). Some studies found statistically significant impacts of age at exposure (Walsh, Tschense et al. 2010, Walsh, Dufey et al. 2010, Tomasek 2012, Tomasek, Rogel et al. 2008) but others did not (Villeneuve, Morrison et al. 2007, Vacquier, Rogel et al. 2009). Attained age was also an important effect modifier

in some studies (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2015, Lane, Frost et al. 2010). Duration of exposure was important in French miners (Vacquier, Rogel et al. 2009) but was not in German miners (Kreuzer, Schnelzer et al. 2010, Grosche, Kreuzer et al. 2006) or in the nested case-control study of Czech, French and German miners (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2015).

Overall, the studies supported the BEIR VI exposure-age-concentration model (National Research Council 1999), with the inverse exposure rate effect disappearing at low cumulative exposures and dose rates (Walsh, Tschense et al. 2010, Walsh, Dufey et al. 2010, Tomasek 2012, Tomasek, Rogel et al. 2008, Vacquier, Rogel et al. 2009, Villeneuve, Morrison et al. 2007, Lane, Frost et al. 2010, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Kreuzer, Fenske et al. 2015). These recent findings were consistent with what was found previously in the joint study of 11 miner cohorts (Lubin, Boice et al. 1995b, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1994, Lubin, Tomasek et al. 1997).

Effect modifiers were not assessed in the Colorado or New Mexico uranium miners or the Swedish iron ore miners (Boice, Cohen et al. 2008, Jonsson, Bergdahl et al. 2010, Schubauer-Berigan, Daniels et al. 2009). Appendix C provides a detailed summary the current literature on potential effect modifiers.

2.5.2 Other risk factors and potential confounding of the radon-lung cancer mortality relationship

Potential confounding risk factors are especially relevant to the radon-lung cancer mortality relationship at low occupational radon exposures since at these low levels, the radon-lung cancer mortality risk relationship is possibly at the limit detectable by current epidemiological methods (Rothman 2002, Rothman, Greenland et al. 2008, Checkoway, Pearce et al. 2004). Any bias in the risk estimates due to confounding will have a greater proportional impact on risk estimates at low radon exposures compared to high radon exposures (Rothman 2002, Rothman, Greenland et al. 2008, Checkoway, Pearce et al. 2004). However, Blair and colleagues argue that examples of substantial confounding are rare in occupational epidemiology. Even in studies of occupational exposures and lung cancer, tobacco-adjusted relative risks rarely differ appreciably from the unadjusted estimates (Blair, Stewart et al. 2007).

A number of known risk factors for lung cancer would ideally be considered for confounder adjustment in the regression modeling of radon exposure effect on lung cancer mortality. These include tobacco smoking and residential radon exposure, other sources of occupational radiation (gamma radiation, long-lived radionuclides (LLR), and other mine-specific hazards (arsenic, silica, diesel exhaust). These risk factors are all classified as carcinogenic to humans (Group 1) (IARC 2012a, IARC 2012b, IARC 2012c, IARC 2013, IARC 1988, IARC 1986). The potential confounding factors of concern in this dissertation and the rationale why they are/are not included as part of the sensitivity analysis of the impact of unmeasured confounders is discussed below and in Appendix B.

2.5.2.1 Tobacco smoking

Tobacco smoking is the primary cause of lung cancer (IARC 1986, IARC 2012b, IARC 1988). Among uranium miners, the prevalence of tobacco smokers has tended to be very high, ranging from about 60% to 90% (Bruske-Hohlfeld, Rosario et al. 2006, L'Abbé, Howe et al. 1991, Leuraud, Billon et al. 2007, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Tomasek 2013, Tomasek 2011, Amabile, Leuraud et al. 2009, Kreuzer, Brachner et al. 2002, Schubauer-Berigan, Wenzl 2001, Villeneuve, Morrison et al. 2007). About 70% of modern uranium miners in Saskatchewan, Canada smoke tobacco (CNSC 2003).

The relationship between radon, tobacco smoking and lung cancer was recently studied in several nested case-control studies of uranium miner studies with extended mortality follow-up (Leuraud, Schnelzer et al. 2011, Tomasek 2011, Tomasek 2013, Hunter, Muirhead et al. 2013, Amabile, Leuraud et al. 2009, Bijwaard, Dekkers et al. 2011, Schnelzer, Hammer et al. 2010, Leuraud, Billon et al. 2007, Bruske-Hohlfeld, Rosario et al. 2006). These studies confirm that the radon-lung cancer mortality relationship persists even when smoking is adjusted for. These findings suggest that results from studies without smoking information are still valid and that smoking does not act as a major confounder in studies of uranium miners. Findings also reflect mainly the risk among smokers since the prevalence of ever smokers is high in uranium miner populations. However, no association could be detected between the proportion of smokers and cumulative exposure to radon progeny (Kusiak, Ritchie et al. 1993). Finally, the ERR/WLM was greater for non-smokers compared to current or ex-smokers, likely reflecting differences in lung morphometry and clearance (Amabile, Leuraud et al. 2009,

Schnelzer, Hammer et al. 2010, Hunter, Muirhead et al. 2013, Bijwaard, Dekkers et al. 2011, Tomasek 2011).

2.5.2.2 Residential radon

Exposure to indoor radon is identified as the main source of natural radiation exposure to the population (ICRP 1993, ICRP 2010, United Nations 2009, WHO 2014) and is considered the second leading cause of lung cancer after tobacco smoking (WHO 2014, WHO 2009, AGIR 2009).

Three large pooled analyses in Europe, North America and China assessed the lung cancer risk due to residential radon (Lubin, Wang et al. 2004, Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005, Darby, Hill et al. 2006, Darby, Hill et al. 2005). If residential radon is estimated to cause between 3 to 14% of all lung cancers, worldwide (WHO 2014), workers' residential radon exposures are likely to impact their overall lung cancer risk. However, the contribution of residential exposure on lung cancer risk among uranium miners has not been assessed. The evidence of an effect from residential radon is generally more difficult to assess because of lower exposures and uncertainties in exposure estimates (Tomasek 2013).

2.5.2.3 Other occupational radiation exposures

A uranium miner's total radiation exposure and corresponding absorbed lung doses come from exposures to internal alpha (α) radiation (radon gas, radon progeny and long-lived alpha emitting radionuclides (LLR) present in the uranium ore dust) and external gamma (γ) radiation in the mine environment (Rage, Vacquier et al. 2012, Marsh, Blanchardon et al. 2012, Marsh, Harrison et al. 2014, Duport 2002).

The potential confounding factors effects of γ-ray and LLR were recently studied in the French (γ-ray and LLR), German (γ-ray and LLR) and Beaverlodge (γ-ray) cohorts. The risk of lung cancer associated with cumulative radon exposure remained significant after taking exposure to γ-ray and LLR into account (Walsh, Tschense et al. 2010, Rage, Caer-Lorho et al. 2014, Vacquier, Rage et al. 2011, Rage, Vacquier et al. 2012, Lane, Frost et al. 2010).

The α-particle radiation accounted for 58% of the total absorbed lung dose and radon progeny accounted for 97% of the α-particle radiation among French miners (Rage, Vacquier et al. 2012, Marsh, Blanchardon et al. 2012, Marsh, Harrison et al. 2014). The short-lived radon progeny, especially polonium-218 (half-life = 3.05 minutes) and polonium-214 (half-life = 1.5×10^{-4} seconds) (refer to Figure 1), were the source of the largest doses of ionizing radiation to lung cells (Bale 1980, Harley 1981, Harley 1952, Harley 1953, Harley 1980). These radon progeny are recognized as the primary sources of the ionizing energy delivered to the respiratory epithelium of the lung by radon (IARC 2012, National Research Council 1991).

This suggested that the confounding effect of LLR (1.3% of the α-particle absorbed lung dose) would be minimal. LLR was found to have a minimal confounding effect on the radon-lung cancer mortality relationship in the French and German cohorts (Walsh, Tschense et al. 2010, Rage, Caer-Lorho et al. 2014, Vacquier, Rage et al. 2011, Rage, Vacquier et al. 2012).

The confounding effect of external γ-ray exposure was less clear. It had minimal confounding effect in the Beaverlodge (Lane, Frost et al. 2010) and German cohorts

(Walsh, Tschense et al. 2010). However, γ-radiation represented 42% of the absorbed lung dose in French miners (Rage, Vacquier et al. 2012) and a confounding effect was found in the French post-1955 sub-cohort. However, the ERR/Gy associated with external γ-ray dose had a strong correlation with the α-particle component of the dose (Rage, Caer-Lorho et al. 2014, Vacquier, Rage et al. 2011, Rage, Vacquier et al. 2012).

2.5.2.4 Non-radiological occupational hazards

Uranium miners may also be exposed to arsenic and silica depending on the mineral content of the ore. They may also be exposed to diesel exhaust from mechanical equipment used in the mines, or other occupational hazards before/after working in a uranium mine.

The International Agency for Research on Cancer (IARC) has classified arsenic and inorganic arsenic compounds as carcinogenic to humans (IARC 2012). Beaverlodge ore was relatively clean with minimal amounts of other carcinogens (arsenic, silica) (Lane, Frost et al. 2010). Similarly, French mines had low arsenic content in the ore. Since it was not an occupational concern it was not measured in French uranium mines (Leuraud, Schnelzer et al. 2011). In the Czech cohort, men who spent more than 20% of their employment at the Jáchymov mine were exposed to the much higher levels of arsenic in the dust at the Jáchymov mine and had clear evidence of a higher risk of lung cancer compared to other miners. However, the radon-lung cancer mortality risk relationship persisted after adjustment for arsenic exposure estimates through stratification (Tomasek, Darby et al. 1994).

Crystalline silica in the form of quartz or cristobalite dust is carcinogenic to humans (IARC 2012). No information on silica exposure was available among Czech uranium miners (Leuraud, Schnelzer et al. 2011). A nested case-control study of French uranium miners found the radon-lung cancer mortality relationship persisted (ERR/WLM = 0.011; 95% CI: 0.003−0.025), after adjustment for silicotic status, a proxy to crystalline silica exposure (ERR/WLM = 0.007; 95% CI: 0.001−0.021) (Amabile, Leuraud et al. 2009).

The International Agency for Research on Cancer (IARC) reviewed the carcinogenicity of exposure to diesel engine exhaust and concluded there is sufficient evidence in humans for the carcinogenicity of this exposure, based primarily on the effect on lung cancer (IARC 2013). Following the IARC decision, the relationship between diesel emissions and lung cancer was reviewed and evaluated by the Health Effects Institute Diesel Epidemiology Panel (2015). They evaluated the lung cancer risk of diesel exhaust among truckers (Garshick, Laden et al. 2012), and underground non-metal miners in the United States (Attfield, Schleiff et al. 2012, Silverman, Samanic et al. 2012, Garshick, Laden et al. 2012). The Panel concluded that the studies met high standards of scientific research and could be useful for estimating lung cancer risks due to the exhaust from older diesel engines (HEI Diesel Epidemiology Panel 2015). However, the increased risk of lung cancer in Swedish iron ore miners could not be explained by diesel exhaust exposure (Bergdahl, Jonsson et al. 2010).

Diesel was introduced into the Beaverlodge mine in the last few years prior to its shut down in 1982 [Mr. Stan Frost, personal communication, 2015-02-11]. No measurements for diesel exhaust were available in the French mines since diesel engines were not introduced until the mid-1970s (Rage, Caer-Lorho et al. 2014). In the Czech uranium

mines, all artificial ventilation was carried out with electric motors; no diesel engines were used (Tomasek, Swerdlow et al. 1994).

Uranium miners could work with other hazardous exposures before or after uranium mining. Since mean duration of employment at a uranium mine is short, hazardous exposures from other employment could have a considerable influence on lung cancer risk. Confounding effects of other gold and hard rock mining experience did not contribute to the radon-lung cancer mortality relationship in a nested case-control study of Beaverlodge miners (L'Abbé, Howe et al. 1991).

2.5.3 Cancers other than lung cancer, and other causes of death

Since 1995, the radon-associated risks for other cancers (especially cancers of the extra-pulmonary system, extra-thoracic airways, leukaemia and lymphomas) have been assessed in updated cohort studies of radon-exposed miners (Schubauer-Berigan, Daniels et al. 2009, Zablotska, Lane et al. 2014, Kreuzer, Walsh et al. 2008, Kreuzer, Grosche et al. 2010, Lane, Frost et al. 2010, Rage, Caer-Lorho et al. 2014, Rericha, Kulich et al. 2006, Kulich, Rericha et al. 2011, Drubay, Ancelet et al. 2014, Dufey, Walsh et al. 2013, Walsh, Dufey et al. 2012, Walsh, Grosche et al. 2015, Kreuzer, Straif et al. 2012, Kreuzer, Sobotzki et al. 2016, Navaranjan, Berriault et al. 2016).

Studies of other causes of death, especially cardiovascular disease and non-malignant respiratory disease among uranium miners are summarized in Appendix D (Kreuzer, Dufey et al. 2013, Kreuzer, Grosche et al. 2010, Drubay, Caer-Lorho et al. 2014, Villeneuve, Lane et al. 2007, Nusinovici, Vacquier et al. 2010, Kreuzer, Kreisheimer et al. 2006, Navaranjan, Berriault et al. 2016).

Excess mortality rates occur among uranium miners for non-lung cancers and other causes of death when compared to an external population. However, there is limited and inconsistent weak evidence that any non-lung cancers or other causes of death are related to uranium miners' occupational radon exposures. Overall, the ability to assess these risks may be limited due to low statistical power due to small numbers of deaths (or cancer incidence), low doses from radon exposures, potential misclassification of primary cancers/causes of death and potential confounding effects from other occupational exposures and tobacco smoking (although Blair and colleagues (2007) argue that examples of substantial confounding are rare in occupational epidemiology). However, the current knowledge of radon associated risk for organs other than the lung does not justify any material changes from the conclusions of Darby and colleagues (Darby, Whitley et al. 1995). The ICRP Publication 115 (ICRP 2010) also concluded that the available epidemiological data shows no consistent evidence for an association between radon concentration and any cancer other than lung cancer.

2.6 Feasibility Study of Saskatchewan Uranium Miners

In 1993, the federal-provincial panel on uranium mining developments examining proposed uranium mines in Northern Saskatchewan recommended that ongoing health studies of past, present and future uranium miners should be conducted (CNSC 2003, CNSC 2015). The panel felt it necessary to study whether working in the uranium industry affects health, especially the association between radon progeny exposure and lung cancer. As a result of the above recommendation, the Saskatchewan Uranium Miner's Cohort (SUMC) study group was formed and included representatives from provincial and federal governments, industry and worker representatives. The SUMC conducted two studies to fulfill its task: Part I was to extend the mortality follow-up of the original Eldorado cohort of uranium miners, which included Beaverlodge mine in Northern Saskatchewan. Part II was an assessment of the feasibility of assessing excess lung cancers in modern miners with relatively low workplace radon progeny exposures (CNSC 2003, CNSC 2015).

The feasibility study was initiated in 2003, with a new cohort of Saskatchewan uranium miners who started working after 1975. This study used provincial cancer rates, age and sex distributions of miners, and current levels of employment, radon and other exposures to assess the radon-lung cancer mortality risk relationship. Contemporary radon-lung cancer mortality risk models (National Research Council 1999, Kusiak, Ritchie et al. 1993) were used at that time and tobacco and residential radon were controlled, to calculate the expected number of excess lung cancers. Based on these risk models, and an estimated 24,000 miners by 2030, a projected 141 lung cancer deaths would occur, primarily from tobacco smoking. Only one person would be expected to have developed

lung cancer from workplace radon, bringing the estimated total to 142 lung cancers deaths. The study concluded it was not feasible to conduct a study of modern miners because exposures are too low (0.13 WLM/year in 2000; 100 to 1,000 times lower than early uranium miners, such as those at Port Radium). It would clearly be impossible to correct for tobacco smoking and residential radon and other potential confounding factors that could confound the study given these predictions (CNSC 2003).

Instead of initiating a new study of modern uranium miners, the CNSC recommended updating the follow-up of existing cohorts of historical uranium miners (i.e., Beaverlodge and Ontario), focusing on miners employed when radiation protections were in place (i.e., forced mechanical ventilation, routine radon progeny monitoring) and cumulative radon exposures were low. These studies would best reflect the radon exposures of modern miners but would have longer term follow-up of exposure histories, and mortality (1950 onward) and cancer incidence (1969 onward) follow-up available to present day.

2.7 Residential Radon Studies

Exposure to indoor radon is identified as the main source of natural radiation exposure to the population (ICRP 1993, ICRP 2010, United Nations 2009, WHO 2014). The largest contributor to indoor radon is radon emissions from the rocks and soil surrounding the home. Other sources include building materials and water; however, these usually contribute very little to the total radon concentration in indoor air (ICRP 1993, ICRP 2010, United Nations 2009, WHO 2014).

Indoor radon concentrations can vary by several orders of magnitude, depending on local geology and environmental factors (United Nations 2009). In the UNSCEAR 2008 Report, the estimated value of worldwide average annual exposure to natural radiation sources was 2.4 mSv. The dose distribution worldwide followed approximately a log-normal distribution, and most annual exposures were expected to fall in the range 1–13 mSv/year. Radon was responsible for approximately 48% (1.15 mSv) of this average annual exposure (United Nations 2010). The range of radon exposures in homes overlaps with the lower range of occupational radon exposures found to cause lung cancer in miners (AGIR 2009).

2.7.1 Studies of residential radon and lung cancer

Since radon was found to accumulate in houses, there was concern about the lung cancer risk of radon in the general population (Lubin, Tomasek et al. 1997). The magnitude of the lung cancer risk from radon exposure in homes was initially extrapolated from studies of high occupational radon exposures in miners, and calculations of radiation dose to different tissues in laboratory animal studies (Lubin, Boice et al. 1995b, National Research Council 1999, Lubin, Boice et al. 1994, AGIR 2009).

However, the assessment of lung cancer risk associated with indoor radon exposure using this extrapolation had substantial uncertainty. Moreover, the generalizability of adult male miners' risk estimates to women and children was limited, because of the influence of heavy smoking among most miners, exposure to other mine contaminants (gamma radiation, long-lived alpha radionuclides, arsenic, silica, diesel exhaust, dust), differences in breathing rates, ventilation patterns, particle size, and other factors (Boice 1997). The period of occupation exposure was also relatively short compared with that over a full life in homes, although the cumulative exposure in mines is generally higher than that in homes (Hunter, Muirhead et al. 2013).

More than 20 separate studies of residential radon and lung cancer have been published since the 1990s. Some studies reported positive or weakly positive findings (Schoenberg, Klotz et al. 1990, Pershagen, Liang et al. 1992, Pershagen, Akerblom et al. 1994), whereas others reported no increased risk (Letourneau, Krewski et al. 1994, Alavanja, Brownson et al. 1994). Thus, taken individually, these studies did not provide conclusive evidence of an association between indoor radon exposure and lung cancer (Lubin, Boice 1997).

An early pooled analysis of three studies found no significant association between residential radon and lung cancer (Lubin, Liang et al. 1994). Subsequently, a meta-analysis of eight case-control studies of residential radon suggested that the risk from indoor radon was not likely to be markedly greater than that predicted from studies of miners (Lubin, Tomasek et al. 1997, Lubin, Boice 1997). The combined trend in the relative risk was just significantly different from zero (two-sided $P = 0.03$); the estimated relative risk was 1.14 (95% CI: 1.0–1.3) at 150 Bq/m^3. However, there were significant

differences in the study-specific estimates of the exposure-response (two-sided; $P < 0.001$) (Lubin, Boice 1997).

Since then, three residential radon pooled analyses have been conducted. These included 13 European studies (Darby, Hill et al. 2006, Darby, Hill et al. 2005), 7 North American studies (Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005) and 2 Chinese studies (Lubin, Wang et al. 2004). Considerable efforts were made to address potential confounding by smoking, including individual smoking histories. The reported increased risks of lung cancer for the European, North American, and Chinese pooled analyses using *measured radon concentrations* gave similar results and were 8% (95% CI: 3−16%), 11% (95% CI: 0−28%) and 13% (95% CI: 1−36%) per 100 Bq/m^3 increase in the long time average radon concentrations, respectively. The increases in risk appeared to be approximately linear with no evidence for a threshold below which there was no risk. The relative risk of radon exposure did not differ significantly with study, age, sex or smoking status in the European pooled analyses (Darby, Hill et al. 2005, Darby, Hill et al. 2006). Likewise, there was no apparent heterogeneity in the association by age, sex, educational level, type of respondent (proxy or self), or cigarette smoking in the North American pooled analyses (Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005).

Since the measured radon concentrations did not take into account year-to-year variability in radon exposure over time, they tend to underestimate the risk of radon-induced lung cancer.

Correcting for random uncertainty in measurements of radon activity concentration, the European pooled analysis was repeated using *detailed long-term average radon*

concentrations, the final estimated risk was 16% (95% CI: 5−31%) per 100 Bq/m^3 increase in long time average radon concentrations (Darby, Hill et al. 2005, Darby, Hill et al. 2006). This was an increase by about a factor of 2 above that found in the same study without correcting for random errors in exposure measurements. The UK Independent Advisory Group on Ionizing Radiation (AGIR) stated that these estimates are perhaps are best risk estimates for lung cancer due to residential radon exposure (AGIR 2009).

Similarly, in the North American studies, used a subset of the data with limited residential mobility and complete radon exposure histories (effectively adjusting for radon measurement error). The ERR = 21% (95% CI: 3–52%) (Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005). This was consistent with the European detailed long-term average radon concentration results. The ICRP stated that an ERR of 16% per 100 Bq/m^3 in air may be considered a reasonable estimate for risk management for residential exposure situations in which the exposure is relatively low and the exposure period is extended over 25 to 30 years (ICRP 2010).

In 2011, Turner and colleagues conducted an analysis of the America Cancer Society Cohort to assess the radon-lung cancer mortality relationship (Turner, Krewski et al. 2011). Mean county-level residential radon concentrations were linked to participants based on residence (ZIP code) enrolment [mean (SD) = 53 Bq/m^3 (38.0)]. Cox proportional hazards regression models and 95% CI were used to obtain adjusted hazard ratios (HR) for the radon-lung cancer mortality association. A total of 3,493 lung cancer deaths were observed among 811,961 participants from 1982–1988. A significant positive linear trend was observed between categories of radon concentration and lung cancer mortality (P = 0.02). A 15% (95% CI: 1–31%) increase in the risk of lung cancer

mortality was observed per 100 Bq/m^3 increase in radon concentration. There was no significant effect modification observed by cigarette smoking status, passive smoking or sulfate air pollution concentration on the additive or multiplicative scale.

Analysis was restricted to individuals who reported living in the same neighbourhood for at least the past 5 years at enrollment (19% (95% CI: 4–36%)). Participants with mean radon concentrations above the Environmental Protection Agency (EPA) guideline value (148 Bq/m^3) had a 34% (95% CI: 7–68%) increase in lung cancer mortality risk relative to those below the guideline value. This large prospective study reinforced the findings of the North American and European combined case-control studies and showed positive associations between mean county-level residential radon concentrations and lung cancer (Turner, Krewski et al. 2011).

In summary, the best lung cancer risk estimate for residential radon remains imprecise; there is heterogeneity between countries and situations, and period effects of tobacco exposure. There may also be systematic changes in residential radon concentrations over time due to increased home energy efficiency. These limitations to our understanding of the effects of domestic radon exposure will partly be addressed by the plan of the World Health Organization and European Commission (including Europe, North America and China) for the world pooling of case-control studies of residential radon and lung cancer that has been underway for more than ten years (WHO 2006).

3 Rationale

In 2015, Canada was the world's second largest uranium producer (in 2009 it was overtaken by Kazakhstan) and accounted for 22% (13,325 tU) of global production (World Nuclear Association 2016). Today, all Canadian mines are in Northern Saskatchewan and production comes mainly from McArthur River and Cigar Lake mines. These are the largest and highest-grade ore deposits in the world. Canada has a significant role in the world's uranium production, with known uranium resources ~494,000 tU as well as continuing exploration (World Nuclear Association 2017).

In contrast, the Czech Republic and France are ranked 13th and 17th in the world with 0.26% (155 tU) and 0.003% (2 tU) of the world's uranium production, respectively, in 2015 (World Nuclear Association 2016). The last underground mine (the Roun mine on the Rožná deposit) is scheduled to close in 2017 in the Czech Republic and uranium mining ended in France in 2001 (World Nuclear Association 2016).

All Canadian uranium mines are regulated through the *Nuclear Safety and Control Act (NSCA)* by the Canadian Nuclear Safety Commission. *Radiation Protection Regulations* are enforced to control and monitor radon levels (and other radiation doses). All nuclear energy workers' doses are monitored, either by indirect area air monitoring or direct monitoring using personal alpha dosimeters (CNSC 2011a). For nuclear energy workers, the effective dose limits are 50 mSv per year and 100 mSv over a 5 year dosimetry period [1 WLM = 5 mSv] (Minister of Justice 1997, Minister of Justice 2000). Canadian uranium miners are exposed to very low levels of workplace radon exposures in uranium mines (i.e., in 2005, the average Rabbit Lake underground miner and McLean Lake mill worker had radon exposures of 0.4 WLM/year and 0.05 WLM/year, respectively). In

addition to ensuring that dose limits are respected, radiation doses are required to be kept As Low as Reasonably Achievable (ALARA), social and economic factors being taken into account (Minister of Justice 1997, Minister of Justice 2000).

Radiation doses are reviewed regularly, quality assessed (starting in 2001), and submitted to Health Canada's National Dose Registry. In 2015, the mean radon progeny exposure of exposed (> 0.0 WLM) uranium mine underground workers was 0.176 WLM (25% quartile 0.040 WLM, 75% quartile 0.250 WLM), as indicated in Table 3-1 .Since underground workers have the highest exposure levels, other workers will have lower exposure. Thus, the exposure of today's uranium miners to radon progeny is very low and is well below the regulatory dose limits (CNSC 2014b, Health Canada 2008).

The historically high levels of radon among past underground miners are known to cause lung cancer (IARC 2012c, IARC 2001, IARC 1988). However; limitations of past cohort studies (i.e., measurement error of radon exposures, cumulative radon exposures > 500 WLM) limits their generalizability to modern miners (Lubin, Boice et al. 1994). Past studies also had limited mortality follow-up and inadequate information on confounding factors.

However, updated cohort studies (based on time periods when radon progeny mitigation programs were implemented, radon exposures were low, and individual radon progeny measurements were of high quality), show the radon-lung cancer risk still exists. This radiation risk needs to be better characterized for today's uranium miners exposed to cumulative low radon exposures and low exposure rates.

Table 3-1 Radon Progeny (WLM) for Uranium Mine Underground Worker 2005–2015 (Health Canada 2016)

Exposure Year	Worker Count	Mean WLM	Mean WLM (> 0)	25% Quartile	50% Quartile	75% Quartile
2005	672	0.106	0.119	0.030	0.080	0.150
2006	775	0.144	0.156	0.030	0.090	0.200
2007	687	0.214	0.222	0.070	0.160	0.305
2008	767	0.176	0.184	0.050	0.130	0.270
2009	831	0.209	0.220	0.050	0.140	0.310
2010	1,125	0.181	0.193	0.050	0.120	0.270
2011	1,203	0.155	0.166	0.040	0.100	0.250
2012	1,292	0.121	0.133	0.020	0.070	0.190
2013	1,566	0.127	0.139	0.040	0.090	0.180
2014	1,121	0.163	0.175	0.040	0.090	0.250
2015	533	0.168	0.176	0.040	0.090	0.250

The workers in this table include uranium mine underground miners, personnel and maintenance job classes.
Special tabulations.

There are few cohorts of uranium miners who were employed when modern radiation protection practices (especially mechanical ventilation and routine radon progeny monitoring) were in place, with high quality information on low cumulative radon exposures, low dose rates, and with accompanying data on confounding factors. However, data from these cohorts of uranium miners are also directly pertinent to the long term health effects of current uranium mining practices. Accounting for potential confounding effects is especially important since any uncontrolled bias could be large relative to the expected effect sizes of radon exposure at low levels. Modifying effects are also not currently fully understood, especially the diminishing of the inverse exposure rate effect at low exposures. Lastly, extended follow-up of existing cohorts will help clarify possible differences in health effects between low occupational and similarly low residential radon exposures. Such work may be used to inform regulatory bodies managing occupational and public standards and regulations.

The current analysis is the first to combine and analyse two European cohorts (Czech, French) and one Canadian (Beaverlodge) cohort of uranium miners with updated long term mortality follow-up. The joint cohort has a large number of uranium miners with low (< 100 WLM) cumulative radon progeny exposures and low (≤ 5 WL) exposure rates. It also has good quality individual radon progeny exposure measurement data which best reflect current occupational radon exposures. The exposure follow-up also represents a time when mechanical ventilation and routine monitoring of radon progeny were in place. The analyses focused on the statistical evidence for a radon-lung cancer mortality relationship and the impact of the modifying effects of attained age, time since exposure windows, and exposure rate. Finally, a sensitivity analysis assessed the impact of unmeasured tobacco smoking on the radon-lung cancer mortality risk estimate

4 Study Objectives

The main objectives were to model:

1. The risk of lung cancer mortality due to < 100 WLM cumulative radon exposure.

2. The impact of effect modifiers on the radon-lung cancer mortality relationship.

3. The impact of unmeasured tobacco smoking on the radon-lung cancer mortality relationship.

5 Methods

5.1 Ethical Considerations

This work was conducted according to accepted ethical practices. The Ottawa Health Sciences Network−Research Ethics Board approved the topic on November 16, 2015 (Protocol # 20150478−01H; *Radon-Associated Lung Cancer Risk at Low Exposures: Beaverlodge, French and Czech Uranium Miners;* renewal expiry date – November 15, 2017).

Data agreements for the use of the Czech, French and Canadian (Beaverlodge) cohorts for this dissertation were signed between Ms. Rachel Lane and a representative of each of the data custodians: the National Radiation Protection Institute (SURO), Czech Republic; the L'Institut de Radioprotection et de Sûreté Nucléaire (IRSN), France; and the Canadian Nuclear Safety Commission (CNSC), Canada. Data agreements were signed on, June 30, 2015, July 8, 2015, and August 4, 2015 respectively.

Amendment to the original ethics approval of Protocol # 2003−0062: The *Eldorado Uranium Miners' Cohort Study Update: Part 1 of the Saskatchewan Uranium Mines' Cohort Study* was not required for the analysis of the Beaverlodge cohort since the type and use of the data for this dissertation was previously approved by Health Canada's Research Ethics Board [R. Carpentier, Research Ethics Board Secretariat, Health Canada, personal communication, 2014-09-10].

5.2 Study Design

The current study is a secondary analysis of previously prepared grouped person-year tables (no individual data was available). The joint cohort includes male uranium mine workers from the Czech Republic, France and Canada (Beaverlodge uranium mine). As the purpose of this study was to assess the lung cancer mortality risk due to low cumulative radon exposures, a decision was made to exclude the years when radon exposure and exposure rates were relatively high and the quality of exposure data was poor. Workers first employed in 1948−1952, 1946−1955, 1948−1964 in the Czech, French and Beaverlodge cohorts, respectively were excluded. Other relevant decisions were made so that the joint cohort follow-up represented the time when mechanical ventilation and routine radon progeny monitoring were in place. The joint cohort improved the precision of risk estimates (i.e., larger combined sample size of individual cohorts, harmonizing the working conditions of the three cohorts, less measurement error because excluded time periods when radon exposures were estimates) and allowed more freedom with statistical modeling. Analyses were initially conducted on each cohort separately to understand both the individual cohorts' characteristics and the influence each cohort would have on the joint analysis. However, the primary analyses were conducted on the joint cohort.

5.3 Data Sources

5.3.1 Study cohorts

This dissertation combines three historical cohorts of underground uranium miners from the Czech Republic (referred to as the Czech cohort), underground miners and open pit miners from France (the French cohort), and underground uranium miners and mill workers from the Beaverlodge mine in northern Saskatchewan, Canada (the Beaverlodge cohort). Data on a total of 20,282 male uranium mine workers were initially available for analysis.

Table 5-1 Number of uranium mine workers in the Czech (1953−1999), French (1956–1999), and Beaverlodge (1950–1999) cohorts

Cohort	Number of mine workers (N)
Czech	7,513
French	3,271
Beaverlodge	9,498
Total	**20,282**

The description of the three cohorts of uranium mine workers, including their exposures, follow-up and outcomes, are presented below. Information on the specific cohorts is described in greater detail in Appendix A.

The Czech cohort included 7,513 male underground uranium miners who started work in mines in two different parts of Bohemia and two different time periods. The older sub-cohort included male uranium miners from the Jáchymov region of west Bohemia (often referred to as the S sub-cohort), who satisfied the following criteria: started work at the mines during 1948–1959; underground work lasted at least four years; and personnel and employment records were available, including details of duration of underground employment and time spent in each shaft (Tomasek, Swerdlow et al. 1994).

The newer sub-cohort included uranium miners from Příbram district mines in central Bohemia (often referred to as the N sub-cohort) who began underground work from 1968−1988, and who worked for at least 1 year (Tomasek 2002, Tomasek, Rogel et al. 2008). Person-years at risk were considered from the beginning of follow-up until the end of follow-up. For the older (S) sub-cohort, miners had to be employed at least four years, and person-years at risk began from the earliest year of follow-up (i.e., 1953) plus four years). In the newer (N) sub-cohort, miners had to be employed at least one year, and person-years at risk began from the earliest year of follow-up (i.e., 1968) plus one year. Thus, start of follow-up was four years and one year after start of employment in the two uranium mine regions, respectively.

The French cohort included 3,271 male uranium miners and open pit miners employed by the Commissariat à l'Energie Atomique (CEA) - Compagnie Générale des Matières Nucléaires Inc. (COGEMA; now known as AREVA NC). Workers had to be employed for at least one year in the period from 1946−1999. The mines were located in four main areas in France (Vendée, Limousin, Forez and Hérault), with different time periods of operation, ranging from 1946−2001. Uranium mining ended in France in 2001. Person-years at risk were considered from the beginning of follow-up until the end of follow-up. The start of cohort entry and follow-up began one year after the date of first employment as a French uranium miner (i.e., person-years at risk began from the earliest year of follow-up – 1956 plus one year) (Vacquier, Rage et al. 2011).

The Canadian cohort (referred to as the Beaverlodge cohort throughout this dissertation) initially included 9,498 male uranium mine workers employed in the Beaverlodge uranium mine, from 1948 to the final shutdown of the mine in June 1982. The

Beaverlodge mine was located outside the community of Eldorado, northern Saskatchewan, Canada. The Beaverlodge cohort is one of three main sub-cohorts in the Eldorado study (1950−1999): the Port Radium cohort of uranium miners from the Northwest Territories, the Beaverlodge cohort of uranium miners from northern Saskatchewan, and the Port Hope radium and uranium refining and processing workers from Ontario. Only the Beaverlodge cohort of uranium miners was included in this dissertation since this sub-cohort represented uranium miners employed after radon mitigation measures were in place, radon measurements were of relatively high quality, and cumulative radon exposures and exposure rates were relatively low.

Person-years at risk were calculated for cohort members from the date of the first day of employment until the end of follow-up. For inclusion in the Eldorado cohort, workers had to be employed some time from 1948−1980, were aged 15−75 years when employed, and were known to still be alive in 1950 at the start of the mortality follow-up (Lane, Frost et al. 2010). For this study, the start of follow-up was the first day of employment for Beaverlodge workers employed from 1965 onward.

5.3.2 Harmonizing the cohorts of uranium miners by time periods of radiation protection measures and quality of radon exposure assessment

Restricted calendar year ranges were established for each cohort. The Czech (1953−1999), French (1956−1999), and Beaverlodge (1965−1999) uranium miner cohorts represented the data sets used for analysis. The time periods chosen corresponded to when workers had better quality occupational exposure information, lower radon exposures and lower exposure rates (Leuraud, Schnelzer et al. 2011). These time periods also corresponded with the introduction of mechanical ventilation systems and other

radiation protection measures, such as routine radon progeny monitoring, that substantially reduced occupational radon exposures (refer to Figure 2).

The years 1953 and 1956 were chosen as the start of the Czech and French cohorts, respectively by the National Radiation Protection Institute, Czech Republic, and the L'Institut de Radioprotection et de Sûreté Nucléaire, France before receipt of the person-year tables used in this dissertation. Workers first employed prior to these years were excluded from the individual cohort data.

In the Czech mines, routine radon monitoring was in place since 1949. In 1953, mechanical ventilation was introduced. Mean annual radon exposure decreased progressively from about 25 WLM/year to 7 WLM/year in the period 1952−1967 and was about 1 WLM/year afterwards (Tomasek, Rogel et al. 2008). In France, radon exposures sharply decreased after 1956, corresponding to changes in radiation protection, such as mechanical ventilation, and systematic monitoring of individual radon exposures. Mean exposures decreased from greater than 20 WLM/year in the period 1946−1955 to less than 4 WLM/year thereafter (Tomasek, Rogel et al. 2008).

In the Beaverlodge mine, mean annual radon exposures decreased from about 50 WLM/year in the 1950’s to about 20 WLM/year in the 1960’s and to less than 3 WLM/year from the 1970’s onward. Personal exposures were assigned, starting with underground uranium miners in November 1966 and expanded to cover all workers in the 1970s (Lane, Frost et al. 2010). The Beaverlodge cohort included workers from the start of the mine’s operation who had high radon exposures, high exposure rates, and low quality exposure information. A decision was taken to include only

person-year data from calendar years 1965 onwards because this time period represented the time period of mechanical ventilation, quality radon measurements, and moderate and low radon exposures (i.e., less than 20 WLM/year).

Table 5-2 Distribution of radon exposures, lung cancer deaths and person-years at risk by calendar year period at risk, Beaverlodge uranium miners

Calendar year period at risk	Mean Cumulative Radon Exposure (WLM)	Standard Deviation (WLM)	Lung Cancer Cases	Person-years
1950–1999	101.1	190.9	279	285,846
1965–1999	98.9	182.0	269	248,580
1970–1999	94.3	173.7	257	223,302

The distribution of mean cumulative radon exposures, lung cancer deaths and person-years at risk for the Beaverlodge cohort by time period is presented in Table 5-2. Only ten lung cancer deaths and 37,265 person-years at risk were excluded from further analysis by restricting the cohort follow-up to post-1965.

Only the person-year tables of the Beaverlodge cohort were available. Thus, excluding calendar years at risk before 1965 still retained post-1965 person-years among workers first hired before 1965 who continued to work after 1965. Only their person-time contributions before 1965 were excluded. This could introduce a potential healthy worker survivor selection bias, by mixing of prevalent and incident hires (Costello, Friesen et al. 2011, Applebaum, Malloy et al. 2007).

Two sensitivity analyses assessed the impact of prevalent hires in the Beaverlodge cohort of this dissertation. The first sensitivity analysis compared the ERR/WLM of Beaverlodge person year restrictions to calendar year periods 1950–1999 (incident hires) and 1965–1999 (includes prevalent hires). In the second sensitivity analysis, it was not possible to determine how many workers started working before 1965 and

continued working after 1965. Although there were few person-years in 1965–1970 with radon exposures received over 10 years prior, a sizable proportion of person-years in 1965–1970 had radon exposures received up to 5 years prior.

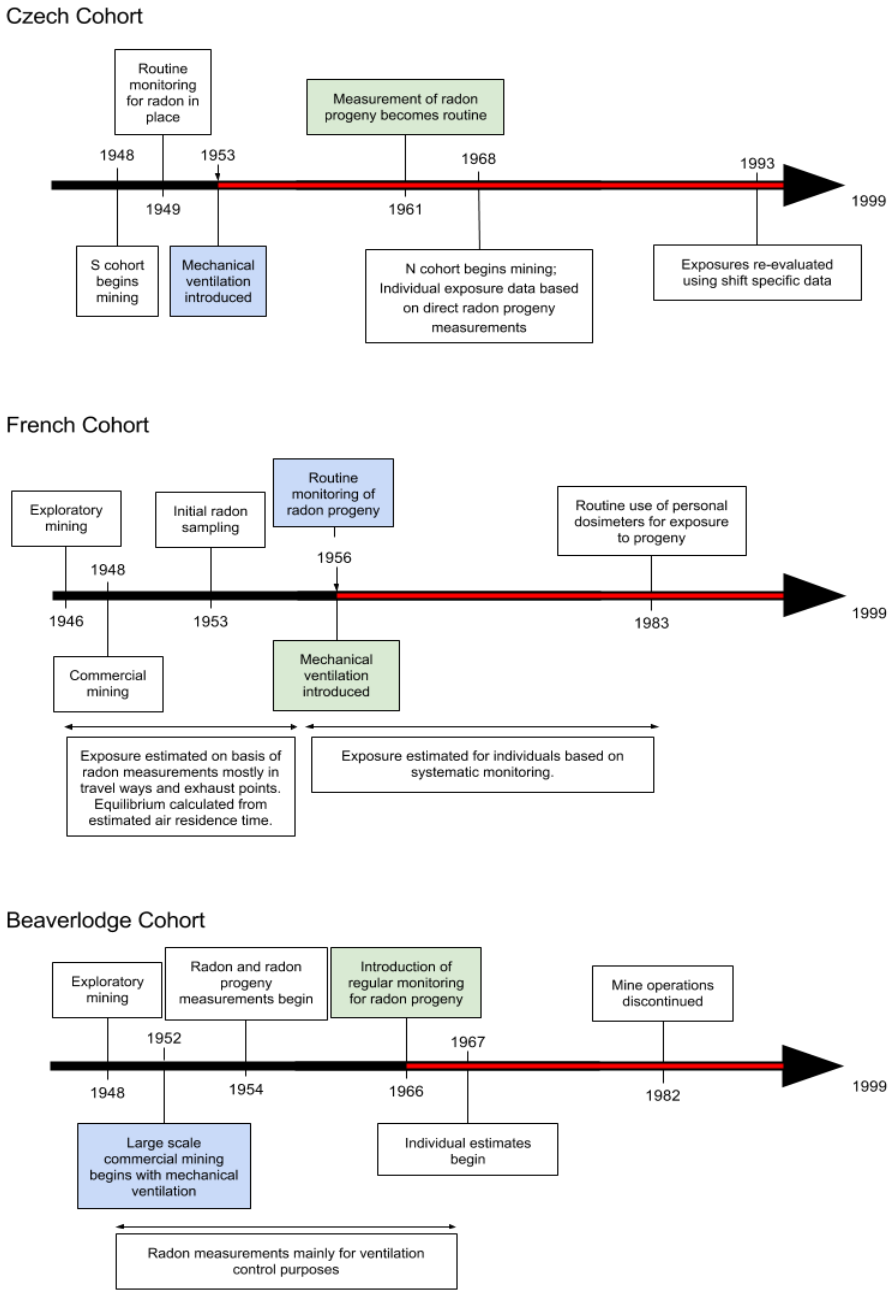

Figure 2 Schedules of Mining Operations and Radon Management for the Czech, French and Beaverlodge Cohorts

Red bar shows the data included in the statistical analysis.
Czech: Follow-up 1953–1999; 196,533 person-years
French: Follow-up 1956–1999; 80,859 person-years
Beaverlodge: Follow-up 1965–1999; 97,617 and 150,964 person-years for < 6 and ≥ 6 months, respectively

5.3.3 Rationale for restricting by duration of employment

The Czech and French person-year tables provided for this dissertation had previously restricted by duration of employment. The Czech cohort only included underground uranium miners from the Jáchymov region and Příbram region who worked for at least four years (Tomasek, Swerdlow et al. 1994) and one year (Placek, Tomasek et al. 1997), respectively. Follow-up started four years after entering the older Jáchymov mines or one year after entering the newer Příbram mines. In the Jáchymov sub-cohort, workers with duration of employment shorter than four years were excluded. This restriction was related to very early analyses of this cohort that found no risk of lung cancer for workers with less than four years exposure [Dr. Ladislav Tomášek, personal communication, March 1, 2017]. The French cohort included uranium miners and open pit miners employed for at least one year. Follow-up began one year after first employment (Vacquier, Rage et al. 2011).

The Beaverlodge cohort did not restrict workers by duration of employment and included all workers on the payroll for one day or more (Lane, Frost et al. 2010). The Beaverlodge cohort was initially stratified by workers into two categories of total duration of employment: those employed less than six months or employed at least six months.

The total length of employment of Eldorado workers (including Beaverlodge and Port Radium uranium mines and the Port Hope radium and uranium refining and processing facility) was significantly associated with the risk of lung cancer mortality (Lane, Frost et al. 2010). Among Eldorado workers with similar radon exposures, those who worked less than six months had a 1.31 times higher risk of lung cancer than those who worked more than six months (95% CI: 1.07–1.60, $P = 0.009$) (Lane, Frost et al. 2010). Thus, the

Eldorado study was stratified by duration of employment (< 6 months and ≥ 6 months employment).

Tabulations of duration and person-years of employment were evaluated to determine if Beaverlodge workers (1965–1999) with less than six months employment should be excluded from further analysis. This was done to assess a potential healthy worker survivor bias (refer to Appendix E) among short term workers as well as to better align with the Czech and French cohorts. In Table 5-3, workers employed less than six months contributed 74 lung cancer deaths (27.5 %) and 97,617 person-years of risk (39.3%) to the Beaverlodge cohort. These workers were younger than longer term workers; 22.7% of their person-years at risk occurred between ages 16−29 years compared to only 4.8% among workers employed at least six months. Likewise, 87.9% (85,838) of their person-years at risk occurred at cumulative radon exposures < 5 WLM, compared to 45.3% (68,292) among workers employed at least six months.

Crude lung cancer mortality rates per 100,000 population were 75.81 for Beaverlodge workers employed less than six months and 129.17 for those employed at least six months (Table 5-4). Likewise, Beaverlodge workers employed at least six months, with < 100 WLM and < 50 WLM had crude lung cancer mortality rates of 91.71 and 80.48 respectively. Although those employed less than six months do not have higher crude lung cancer mortality rates and may not introduce a healthy worker survivor bias, they had very low mean cumulative exposures (9.97 WLM (SD = 15.414, range 0–99.5 WLM). Thus, Beaverlodge workers employed for less than six months were excluded from further analyses to be more consistent with the exclusion criteria used in the Czech and French cohorts.

Table 5-3 Distribution of lung cancer deaths and person-years at risks of the Beaverlodge cohort (1965−1999) by duration of employment

Variable	Duration of Employment					
	< 6 months		6 months+		Total	
Lung cancer deaths	74		195		269	
Person-years at risk						
Age at risk	**Person-years at risk**	**%**	**Person-years at risk**	**%**	**Total**	**%**
16–29	22,189	22.7%	7,209	4.8%	**29,398**	**11.8%**
30–39	25,097	25.7%	34,155	22.6%	**59,252**	**23.8%**
40–49	22,227	22.7%	43,874	29.0%	**66,101**	**26.6%**
50–59	15,749	16.2%	35,843	23.8%	**51,592**	**20.8%**
60–100	12,356	12.7%	29,882	19.8%	**42,238**	**17.0%**
Total	**97,617**	**100.0%**	**150,964**	**100.00%**	**248,580**	**100.0%**
Calendar year period at risk						
1965–1969	11,249	11.5%	14,029	9.3%	**25,278**	**10.2%**
1970–1979	27,436	28.1%	35,777	23.7%	**63,212**	**25.5%**
1980–1989	34,138	35.0%	49,289	32.6%	**83,428**	**33.6%**
1990–1999	24,794	25.4%	51,869	34.4%	**76,663**	**30.8%**
Total	**97,617**	**100.0%**	**150,964**	**100.0%**	**248,580**	**100.0%**
RDP exposure (WLM)						
0.0	26,480	27.1%	18,369	12.2%	44,850	18.0%
> 0.0–4	59,358	60.8%	49,923	33.1%	109,281	44.0%
5–9	5,770	5.9%	15,842	10.5%	21,613	8.7%
10–19	2,702	2.8%	17,354	11.5%	20,056	8.1%
20–39	2,850	2.9%	16,337	10.8%	19,187	7.7%
40–99	457	0.5%	16,287	10.8%	16,744	6.7%
100–1,617.0	0	0.0%	16,851	11.2%	16,851	6.8%
Total	**97,617**	**100.0%**	**150,964**	**100.0%**	**248,580**	**100.0%**

Cumulative radon exposure is weighted by person-years at risk.WLM, working level months.

Table 5-4 Mean cumulative exposure, lung cancer deaths, person-years at risk and crude mortality rate by duration of exposure for the Beaverlodge cohort (1965−1999)

Duration of Employment		Mean cumulative exposure (WLM)	Lung cancer deaths	Person-years	Mortality rate (per 100,00)
< 6 months	Total	9.97	74	97,617	75.81
6 months +	Total	118.5	195	150,964	129.17
	< 100 WLM	32.3	123	134,113	91.71
	< 50 WLM	19.5	100	124,247	80.48

Cumulative radon exposure is weighted by person-years at risk.WLM, working level months.

5.3.4 Rationale for including open pit miners and mill workers in addition to underground uranium miners

This dissertation includes various job categories of uranium mine workers: The Czech cohort included only underground miners, the French cohort included open pit miners, and the Beaverlodge cohort included mill workers (designation as an underground miner or a mill worker reflected the job held for the longest time) (Lane, Frost et al. 2010, Vacquier, Caer et al. 2008, Tomasek, Rogel et al. 2008). Open pit miners and mill workers accrue less radon exposures than underground miners who have the highest radon exposures in the mining job sector (Health Canada 2008). Workers with less strenuous above-ground jobs may be systematically different than underground miners (i.e., too sick to do the strenuous work of underground miners) and could cause a healthy worker survivor bias (refer to Appendix E).

Unfortunately, the job categories of workers were not included in the data set provided for this dissertation. However, a previous analysis that compared standardized mortality ratios (SMRs) of the Beaverlodge cohort with the general Canadian male population found underground uranium miners had a significant excess of lung cancer (SMR = 1.6; 95% CI: 1.4–1.9; $P < 0.001$, N = 198), whereas mill workers had lower but statistically non-significant mortality rates (SMR = 0.9; 95% CI: 0.5–1.3, $P = 0.507$, N = 24) compared to the general male population. Mill workers had statistically significant lower mortality rates for all-cause mortality (SMR = 0.8; 95% CI: 0.6–0.9, $P = 0.003$, N = 247) and statistically non-significant lower mortality rates for all cancers combined (SMR = 0.8; 95% CI: 0.6–1.9, $P = 0.094$, N = 68) compared to the general male population. Unfortunately, an exposure-response analysis of the radon-lung cancer mortality relationship by job category was not conducted (Lane, Frost et al. 2010).

Table 5-5 Standardized mortality ratios (SMR) and 95% confidence interval compared to Canadian mortality rates (1950−1999) for selected causes; males, Beaverlodge cohort (CNSC 2006)

Cause	Job Category	Observed deaths	Expected deaths	SMR	95% CI	*P*−value
All causes	All	2,289	2,311.3	1.0	1.0−1.0	0.653
	Underground workers	1,348	1,244	1.1	1.0−1.1	0.004
	Mill workers	247	297.6	0.8	0.7−0.9	0.003
All cancers	All	635	646.1	1.0	0.9−1.1	0.681
	Underground workers	395	354.1	1.1	1.0−1.2	0.034
	Mill workers	68	83.5	0.8	0.6−1.0	0.094
Lung cancer	All	279	217.8	1.3	1.1−1.4	< 0.001
	Underground workers	198	120.7	1.6	1.4−1.9	< 0.001
	Mill workers	24	28.1	0.9	0.5−1.3	0.507

Adjusted for age and calendar year at risk.

A previous analysis of the French cohort from 1946−1999 found that mine type appeared to be a modifying factor (open pit ERR/WLM = - 0.0024; $P = 0.02$; underground ERR/WLM = 0.0077) in the radon-lung cancer mortality relationship. However, a follow-up analysis performed only with miners employed after 1955 showed no significant effect with mine type (Vacquier, Rogel et al. 2009). Since the French and Beaverlodge analyses did not indicate that above-ground uranium mine workers were less healthy than underground workers, they were included for further analysis.

5.3.5 Primary outcome – lung cancer

Lung cancer death was the primary outcome of interest. The International Classification of Disease (ICD) codes (WHO 1998) were used to code and classify mortality data from death certificates. In the Czech and French cohorts, all causes of death were coded according to the International Classification of Diseases, 8th revision (ICD8) before 1978 and the 9th revision (ICD9) afterward. Lung cancers in both the cohorts were all primary lung cancers (ICD8 and ICD9 coded as 162 before 1994 and C33 and C34 since 1994) according to death certificates. No histology confirmation was available in the French

cohort. In the Czech cohort, histology was available for about 85% of lung cancers. Carcinoid tumors were not included among lung cancers (Tomasek, Rogel et al. 2008, Vacquier, Rage et al. 2011). In Canada, original ICD codes for underlying cause of death of lung cancer were recoded to the ICD 9th revision (Lane, Frost et al. 2010).

5.3.6 Mortality follow-up

Vital statistics for the Czech cohort were obtained from the Czech Population Registry at the Ministry of the Interior. Cause of death information came from local death registries before 1982. After 1982, this information came from the Institute of Health, Information and Statistics of the Czech Republic. The proportion of missing causes was 0.4% and was similar throughout the calendar periods (Tomasek, Rogel et al. 2008).

In France, vital statistics were initially obtained from the administrative and medical files of Compagnie Générale des Matières Nucléaires Inc. For each miner suspected to have died or with an unknown status, vital status was obtained from the town hall of his place of birth (if born in France), or the Ministry of Foreign Affairs (if born outside France). For deaths prior to 1968, the cause of death was obtained from the occupational medical records of COGEMA and 32% of causes of death were missing. After 1968, only about 5% of causes of death were missing. The cause of death was obtained from a standardized anonymous linkage procedure of the French national mortality database (direct or initial cause of death, as well as two preceding or underlying causes or morbid conditions that contributed to death), supplemented by information from the COGEMA occupational medicine department (Vacquier, Rage et al. 2011). Information for this database is collected from death certificates.

The person-years for France were corrected to adjust for 32% missing causes of death in France before 1965, and 28% missing causes of death from 1965−1969 prior to when the national mortality database existed. Since the French follow-up data (in tabulated form) are organized by 5 year categories, the proportion of missing causes before 1965 is 32%, and in the calendar period 1965−1969 the missing causes proportion is a mixture of 32% before 1968 and 5% after, resulting in 28% for the whole period 1965−1969. The correction for missing causes was applied as the lung cancer death rates in early years would be otherwise underestimated (Tomasek, Rogel et al. 2008).

In Canada, vital statistics were obtained from Statistics Canada, through a series of record linkages of the Beaverlodge cohort (CNSC 2004). The cohort was first linked to the Historic Tax Summary file (available from 1984−2000) to determine if workers were alive at the end of follow-up, which was December 31, 1999. This linkage was done on only 60% of Eldorado workers since a social insurance number (SIN) was required for this linkage. The SIN was created in 1964 in Canada so no Port Radium workers (1942-1960) would have a SIN. However, Revenue Canada started using the SIN for mandatory tax reporting purposes in 1967 (Office of the Privacy Commissioner of Canada 2014) so most Beaverlodge workers from 1965 onward had a SIN. Additional identifying information from the tax summary file substantially improved the quality of subsequent record linkages. Next, the cohort was linked to the Canadian Mortality Database (CMDB) from 1950−1999 via probabilistic record linkage (Howe 1998) to obtain death information. This database contains records of all deaths registered in Canada and voluntarily reported deaths of Canadian residents occurring in the United States. The cause of death was available since 1950. Data in the mortality database are obtained

through the vital statistics system for national reporting of vital statistics data. Since the registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, reporting is virtually complete. Under-coverage of death records is thought to be 1% or less (Goldberg, Carpenter et al. 1993). Finally, cancer incidence was determined through probabilistic record linkage of the nominal roll file to the Canadian Cancer Database (CCDB) from 1969–1999, for the entire Eldorado cohort linkage (not specifically for this dissertation). Data in the CCDB are obtained from provincial and territorial cancer registries and are essentially complete for all cases of cancer occurring in Canada (www.naaccr.org/). This database contains records of all cancer cases diagnosed in Canada among people who reside in a province/territory at the time of diagnosis and voluntarily reported cases of Canadian residents diagnosed in the United States since 1969 (Statistics Canada 2014).

While cancer incidence was not assessed in the joint cohort study for this dissertation, this linkage helped to improve the quality of the mortality linkage by validating or adding identifying variables, lung cancer diagnosis and histology, if available. All this information helped validate the lung cancer deaths ascertained by the CMDB in the Beaverlodge cohort.

5.3.7 Rationale for restricting workers by age

In the Czech and French cohorts, follow-up was censored at age 85 to reduce potential bias due to missing information and uncertainty of diagnoses in older age categories (Tomasek, Rogel et al. 2008). A relatively high proportion of misclassified causes of death have been documented in older workers (Rage, Vacquier et al. 2012). Follow-up in the Beaverlodge cohort was censored at age greater than 100 years if no death was found (Lane, Frost et al. 2010). Misclassification of lung cancer deaths from age 85 to 100 years is unlikely because of Canada's high quality cancer incidence (www.naaccr.org/) and mortality (Goldberg, Carpenter et al. 1993) databases and the use of multiple linkages (Historic Tax Summary File, CMDB, CCDB), and the manual resolution of potential computer links. Although there were 0 deaths, there were 650 person-years overall and 485.3 person-years <100 WLM cumulative radon exposures for Beaverlodge workers aged 85−100 years (Table 5–6**.**). This age group had little impact on risk estimates so it was not excluded from analysis.

Table 5-6 Lung cancer deaths and person-years at risk among uranium miners age 80-100 years

Sub cohort	Age category	Total Cumulative Exposure		Cumulative Exposure < 100 WLM	
		Lung Cancer Deaths	Person-years	Lung Cancer Deaths	Person-years
Czech	80-84	2	195.7	2	181.8
French	80-84	0	118.2	0	118.2
Beaverlodge	80-84	3	944.27	3	729.1
	85-100	0	650.0	0	485.3
Total		**5**	**1,908.17**	**5**	**1,514.4**

5.3.8 Radon exposures

Figure 2 illustrates the schedules of mining operations and radon management for the Czech, French and Beaverlodge cohorts.

In the Czech cohort, the Jáchymov (S) sub-cohort, extensive radon exposure data were available from 39 000 measurements of radon gas concentrations and other potentially hazardous material taken underground during 1949 to 1963 (most shafts at Jáchymov closed in 1963). Each miner's annual exposure to radon progeny was estimated by combining measurement data with the registered details of his employment, including duration of underground work in different shafts and job category (Tomasek, Swerdlow et al. 1994). On average, 200 radon measurements per shaft were made each year to the end of 1960 and more than 900 afterward. Annually, the number of measurements varied from 100 to 700, proportional to the number of miners working in various areas (Sevc, Kunz et al. 1976, Kunz, Sevc et al. 1978, Kunz, Sevc et al. 1979, Tomasek, Darby et al. 1993, Tomasek, Swerdlow et al. 1994, Tomasek, Darby et al. 1994, Sevc, Tomasek et al. 1993).

In 1953, natural ventilation was augmented by a mechanical (forced air) ventilation system. Estimates of radon progeny exposure were based on radon gas concentrations. The concentrations of radon gas were converted to concentrations of radon progeny using measurements of equilibrium factors in mines when mechanical ventilation was not operated for one month. Each miner’s annual exposure to radon progeny was estimated, combining measurement data with registered employment details, including duration of underground work at different shafts and job categories. Radon progeny concentrations

were first measured in 1961. From 1961−1969 the mean number of annual radon progeny measurements recorded per shaft was over 900, about 3 per work day (Sevc, Kunz et al. 1976, Kunz, Sevc et al. 1978, Kunz, Sevc et al. 1979, Tomasek, Darby et al. 1993, Tomasek, Swerdlow et al. 1994, Tomasek, Darby et al. 1994, Sevc, Tomasek et al. 1993).

The Příbram (N) sub-cohort of Czech uranium miners represented mining employment from 1968−1988. Individual exposure data (direct radon progeny measurements in ambient air) were made from 1968 onward (Placek, Tomasek et al. 1997). In some shafts, measurements were not available in the first few years of operation, so exposure data were extrapolated from later data.

In addition, some miners in both sub-cohorts also worked in non-uranium mines. These non-uranium mine radon exposures (substantially lower) were derived from radon measurement in the mid 1960's in non-uranium mines (Sevc, Cech 1966). Such exposures were classified as estimated.

The estimation of individual exposure made use of information on the job in each year and month worked. Non-hewer jobs (maintenance, support, technical, supervising underground workers) had about half the exposure of hewers (general miners working at the mine face or stopes, including drillers and muckers). A job exposure matrix was derived from data for the Příbram (N) sub-cohort (Tomasek, Rogel et al. 2008). Exposures were considered high quality if based on annual estimates of current ambient measurements or personal dosimetric records per year. Exposures retrospectively estimated or extrapolated were considered of lower quality (Tomasek, Rogel et al. 2008).

In the French cohort, mechanical (forced air) ventilation was introduced in each mine in 1956. At the same time, an increase in the number of ambient measurements and the systematic control of individual radiation exposure began. This resulted in a sharp decrease in annual exposures. From 1956–1982, exposure for each miner was routinely recorded on a monthly basis from the measurements of ambient radon gas concentrations at work sites, adjusted for time worked. Between 20,000 and 50,000 measurements were made each year. In addition to these gas measurements, several hundred measurements of potential alpha-particle energy concentrations (PAEC) were performed in different French mining divisions and were used to derive the equilibrium factor. For each miner, exposures were recorded monthly, based on measurements of radon concentration at working locations, time worked and the type of job. Since 1983, individual radon exposures were determined directly from individual alpha dosimeters. These measured both radon gas concentration and potential alpha-particle energy concentration (PAEC) due to short-lived radon progeny and therefore allowed estimation of the equilibrium factor. The mean equilibrium factor was 0.22 (Leuraud, Schnelzer et al. 2011, Vacquier, Rage et al. 2011, Tomasek, Rogel et al. 2008).

In the Beaverlodge mine, a mechanical (forced air) ventilation system was used underground from the time it started operation to ensure that exposure to radon gas and its radioactive progeny was as low as possible [Mr. Stan Frost, personal communication, 2015-10-07]. Both radon and radon progeny measurements were started in 1954 and continued at increasing frequency throughout the mine's operation. The total number of radon measurements per work area per year from 1954−1968 was generally less than 12, with an average of about four measurements per work area per year. The concentrations

of radon gas measurements were converted to radon progeny concentrations using equilibrium factors determined in 1954, 1956, 1959 and 1961 through paired measurements of radon and radon progeny concentrations (Lane, Frost et al. 2010). Personal exposures were assigned, starting with underground miners in November 1966 and expanding to cover all personnel in the 1970s (Lane, Frost et al. 2010).

Prior to the assignment of individual exposures, annual individual radon progeny exposures were originally estimated, using the annual geometric mean radon progeny concentrations underground and in the mill and time spent in the workplace. The annual mean for these workers was recalculated by summing over the exposure rate (WL) measurements available for each type of workplace, the proportion of employees in each occupation, and the proportion of time spent in each type of workplace by employees in each occupation (SENES Consultants Limited 1996).

The National Dose Registry had no early records from Eldorado Mining and Refining and no records for any of the other early Canadian mines. Many Beaverlodge workers' records also indicated prior mining experience in other early Canadian mines. For these workers, their other mine exposure levels were estimated from the Beaverlodge data (SENES Consultants Limited 1996). Thus, there was likely mismeasurement of exposure for a sizeable portion of the early years of uranium mining. (Lane, Frost et al. 2010).

Finally, Beaverlodge workers also obtained employment in other Canadian mines/industries with potential radiation exposure after leaving Eldorado Mining and Refining. The National Dose Registry collected and recorded radiation exposure and dose data for all radiation exposed workers in Canada from 1951 (with some records going

back to 1944) (Health Canada 2008). For all other non-Eldorado radiation exposures in Canada, the Beaverlodge cohort was linked to the National Dose Registry from 1951−1999) (Health Canada 2008).

5.3.9 Rationale for including workers with 0.0 WLM cumulative exposures for baseline exposure

Another consideration was the appropriateness of using 0.0 WLM as the baseline exposure category for the radon-lung cancer mortality exposure-response relationship. If workers with zero cumulative exposures were systematically different from workers with higher cumulative exposures, another baseline exposure category could be more appropriate.

The 2001 Report on Occupational Radiation Exposures in Canada (Health Canada 2001) provides information on all radiation workers in Canada. The uranium mining sector included 14 job categories: electrician, mill maintenance, mill worker, nurse, office staff, support worker, surface maintenance, surface miner, surface personnel, surface support worker, underground maintenance, underground miner, underground personnel, and visitor.

In 1999, the mining job sector included 2,471 workers with an average annual dose of 1.08 mSv (63.8% radon progeny). For all job categories, the five year period 1995−1999 average dose was greater than 0.0 mSv. Job categories had different average radiation doses. For example the average dose for the five year period 1995−1999 ranged from 0.15 mSv (83% radon progeny) for a uranium mine nurse to 9.99 mSv (47% radon progeny) for an underground uranium miner (Table 5-7). All job categories included some workers with zero average annual exposures, including underground miners. Thus,

workers with zero cumulative radon exposures were not systematically different from those with greater than zero exposures, so 0.0 WLM cumulative exposure was retained as the baseline exposure category.

Table 5-7 Occupational radiation exposures for uranium mine underground miner and uranium mine nurse for the year 1999 and the five year period 1995–1999, Canada (Health Canada 2001)

	Uranium Mine Underground Miner		**Uranium Mine Nurse**	
Time Period	1999	1995–1999	1999	1995–1999
Number of workers with 0.0 mSv dose	14	32	17	22
Total Number of workers	341	971	22	31
Average Dose (mSv)	2.60	9.99	0.05	0.15
% Radon Progeny	63%	47%	71%	83%

5.4 Checking and Editing Data

The data obtained for this dissertation were based on non-identifiable person-year tables, not individual data. The identification and elimination of duplicate and invalid records, recoding of disease codes over time, and editing of the non-identified individual records (i.e., of missing values, such as date fields) was completed for all three cohorts prior to undertaking this dissertation (Lane, Frost et al. 2010, Vacquier, Rage et al. 2011, Tomasek, Rogel et al. 2008). Thus, no further data editing was undertaken for the current analyses.

Data processing of the entire Eldorado cohort (not specific to Beaverlodge) led to the exclusion of 2,195 (11.0%) records. The final cohort for mortality analysis consisted of 17,660 subjects (88.9% of the original cohort), of which 9,498 were male Beaverlodge uranium miners (Lane, Frost et al. 2010). Although information on missing data specific to Beaverlodge is not available, it is likely that the completeness of data for workers employed in Beaverlodge improved with time. It is also likely that Port Radium workers had the greatest amount of missing data (especially date of birth, which is an important identifying variable) because the mine started prior to when record keeping was required for regulatory purposes. Missing data on Beaverlodge workers would have been most likely to arise prior to 1964, before the social insurance number (SIN) was implemented in Canada.

A description of the checking and editing of data was not available for the French or Czech cohorts.

5.5 Statistical Analysis

The primary analyses in this dissertation are internal cohort comparisons in which Poisson regression methods have been applied to detailed tabulation s of deaths and person-years at risk (Preston 1996). Thus, analyses were conducted using internal linear Poisson regression modeling with grouped cohort survival data (Breslow, Day 1987, Preston, Lubin et al. 1993). This involved treating the observed number of lung cancer deaths as a Poisson distributed variable in a number of cells formed by cross classification. Grouped data on individual members of the cohort were cross-classified on several time scales and other relevant explanatory variables: sub-cohort, age at risk, calendar year period at risk, cumulative radon exposure, age at first radon exposure, and time since first radon exposure, exposure rate.

The basic data in each cell of this cross classification are the person-years at risk (denominator) and the observed number of lung cancer deaths (numerator), which together comprise an observed mortality rate, lung cancer deaths/ person-years at risk. The resulting rates were then modeled as a function of explanatory variables (Breslow, Day 1987).

This dissertation did not test for over-dispersion when fitting the Poisson models. Follow-up time in each stratum of grouped person-years is not constant for individuals, and so the counts of death will not necessarily follow a Poisson distribution. However, the Poisson assumption will still be approximately correct because deaths are rare in each stratum (Breslow, Day 1987).

5.5.1 Rationale for lagging to control healthy worker survivor effect

Cumulative radon exposures were lagged by five years to account for a possible minimal induction time and to control for issues of "reverse causality" where changes in job status among workers could be due to undetected or early stage lung cancer (Buckley, Keil et al. 2015, Gilbert 1982). The "at risk" person-time that a worker spent at a radon exposure level could begin to accumulate as soon as the radon level was reached and the five year lag period had passed. Thus, for each year of follow-up, radon exposures within the previous five years were assumed to be unrelated to the risk of lung cancer mortality and were ignored when computing cumulative radon exposure. A five-year lag interval has a strong theoretical base with strong empirical support (IARC 1988, Hornung, Meinhardt 1987, Lubin, Boice et al. 1994). It has been used in the extended follow-up of recent cohort studies of uranium miners (Kreuzer, Fenske et al. 2015, Vacquier, Caer et al. 2008, Tomasek 2012, Lane, Frost et al. 2010).

5.5.2 Calculation of age- and calendar- period specific person-year tables

Due to confidentiality restrictions under the Canadian Statistics Act, only aggregate person-year tables of the Beaverlodge cohort were released from Statistics Canada for use. The Beaverlodge person-year tables were prepared by Dr. Lydia Zablotska for the Eldorado cohort study. Aggregate person-year tables were provided separately for the Czech, French and Beaverlodge cohorts. Initial work using the non-identifiable individual data was required to structure the Czech and French cohorts' person-year tables to ensure they were aligned with the Beaverlodge categorization. Dr. Ladislav Tomášek prepared the Czech and French person-year tables used in this dissertation.

For all miners, person-years were accumulated from the date of entry into the cohort (i.e., the start of follow-up). This was the first day of employment for the Beaverlodge workers, the date of first employment plus one year for the French workers, and either the date of first employment plus four years for the older Jáchymov (S) sub-cohort, or the date of first employment plus one year for the newer Příbram (N) sub-cohort of the Czech cohort (Lane, Frost et al. 2010, Tomasek 2012, Vacquier, Rage et al. 2011).

In the Czech and French cohorts, each individual contributed person-years at risk from the start of follow-up, to the earliest of the date of death, emigration (Czech), loss to follow-up, age 85 years, or December 31, 1999, which was the end of the study period (Vacquier, Rage et al. 2011, Tomasek, Rogel et al. 2008).

In the Beaverlodge cohort, each individual contributed person-years at risk from the start of follow-up, to the earliest of the date of death, the last date known alive (defined as the date of last employment or contact), or December 31, 1999, which was the end of the study period (Lane, Frost et al. 2010).

The summary person-year experience for the Czech and French cohorts was cross-classified into 12 strata of age at risk (five year intervals: ≤ 29, 30−34... 75−79, 80−84), and 9 strata of calendar year period at risk (five year intervals: 1955−1959, 1960−1964... 1990−1994, 1995−1999), with each stratum further described by mean cumulative radon exposure (lagged five years), mean age at first radon exposure, and mean time since first radon exposure.

The summary person-year experience for the Beaverlodge cohort was cross-classified by 13 strata of age at risk (five year intervals: ≤ 29, 30−34... 75−79, 80−84, 85−100), and

7 strata of calendar year period at risk (five year intervals: 1965−1969, 1970−1974...1990−1994, 1995−1999), with each stratum further described by mean cumulative radon exposure (lagged five years), mean age at first radon exposure and mean time since first radon exposure (Lane, Frost et al. 2010).

For the joint cohort, the summary person-year experience was cross-classified by three sub-cohorts (Czech, French, Beaverlodge), and standardized strata: 12 strata of age at risk (five year intervals: ≤ 29, 30−34, 35− 39, 40−44, 45−49, 50−49, 55−59, 60−64, 65−69, 70−74, 75−79, 80−100), and 9 strata of calendar year period at risk (five year intervals: (1955−1959, 1960−1964, 1965−1969, 1970−1974, 1975−1979, 1980−1984, 1985−1989, 1990–1994, 1995–1999). Beaverlodge had no accumulated person-years in the calendar years 1955−1959, 1960−1964 because the start date for this dissertation was calendar year 1965−1969 onward.

5.5.3 Excess relative risk models

Internal linear Poisson regression, for grouped survival data, was used to fit excess relative risk models using background stratification rather than covariate adjustment to control for confounders (Richardson, Langholz 2012). Maximum likelihood parameter estimates (MLE), likelihood ratio tests for nested models, and likelihood-based confidence intervals were derived. Deviance was used as an overall measure of model fit. For nested models, the difference in the deviance between the two models provides the basis for a likelihood ratio test, with degrees of freedom equal to the number of added parameters (Lubin, Boice et al. 1994).

A linear Poisson model was fit, such that:

$$\boldsymbol{Rate_w = Rate_0 \times (1 + \beta w)} \quad \textbf{(1)}$$

Where $Rate_w$ is the lung cancer mortality rate at cumulative exposure w, where w is the five-year lagged exposure, in WLM. $Rate_0$ is the background lung cancer mortality rate, stratified to control for confounding by three strata of sub-cohort (Czech, French, Beaverlodge), 12 strata of age at risk (≤ 29, 30−34... 75−79, 80−100), and 9 strata of calendar year period at risk (1955−1959, 1960−1964...1990−1994, 1995−1999).

In this model, β estimates the ERR per unit of cumulative radon exposure w in WLM and where w is taken to be a continuous variable. Adding 1.0 to the ERR/100 WLM results in the RR at 100 WLM of cumulative radon exposure.

In this dissertation, the continuous exposure-response analyses (ERR/WLM) for the radon-lung cancer relationship were conducted for the three cohorts separately and as a joint cohort. The focus of the analyses was on lung cancer mortality at cumulative radon exposures of < 100 WLM and < 50 WLM (5-year lagged).

Similar to the approach taken for the 11-cohort analysis (Lubin, Tomasek et al. 1997), for time-varying factors, workers contributed to the appropriate category as time progressed. Thus, most miners, regardless of their final cumulative exposures, contributed person-years to the restricted exposure dataset. Therefore, the restricted analysis (< 100 WLM) includes all person-years, deaths, cumulative exposures (5-year lagged), and other time-dependent covariates (age at risk, calendar year period at risk, etc.) that occurred up to this exposure cut point. This includes information from all workers up to this cut point, even if their cumulative exposures are ≥ 100 WLM. As indicated in Table 6-3, the < 100 WLM restricted analysis includes 394,236 (92%) of person-years and 408 (63%) lung

cancer deaths. Workers with ≥ 100 WLM cumulative exposures (5-year lagged) have an additional 34,120 person-years (428,356-394,236) and 241 lung cancer deaths (649-408) that occurred at ≥ 100 WLM. This information is excluded from the restricted analysis. A similar approach was used for the < 50 WLM restricted analysis (based on 360,370 person-years and 276 lung cancer deaths).

This dissertation also assessed whether parameterization of low cumulative exposure into categories affected the radon-lung cancer relationship. Maximum likelihood estimates for relative risks based on equation (1) were used. Here, *w* represents the five-year lagged mean cumulative radon exposure in each exposure category, stratified by sub-cohort, age at risk and calendar year period at risk. The relative risk in different exposure categories are compared to the baseline category, which represents all workers at 0.0 WLM exposures.

Finer cut points were chosen to distribute lung cancer deaths relatively evenly among < 100 WLM cumulative radon exposures. Analyses were conducted for the three cohorts separately and combined. Categorization of cumulative WLM was unique to each cohort, depending on the distribution of lung cancer deaths in each stratum of cumulative radon exposure. A minimum of five lung cancer deaths were required in each strata. The strata were harmonized in the joint cohort analysis.

5.5.4 Effect modifiers

An exposure-age-concentration model was used to investigate the modifying effects of the radon-lung cancer mortality relationship. This model was first developed by Lubin and colleagues in 1994 and was incorporated into the BEIR VI Committee's model for the risk of lung cancer due to cumulative radon exposure (Lubin, Boice et al. 1994, National Research Council 1999). The impact of effect modifiers on the radon-lung cancer relationship among past miners with low cumulative radon exposures and low exposure rates can be assessed with a modified ERR model:

$$\boldsymbol{Rate_w = Rate_0 \times [1.0 + (\beta w)\, exp\, (\textstyle\sum_i \gamma_i\, z_i)]} \qquad \textbf{(2)}$$

Where z_i are potential modifying factors, such as time since exposure, attained age and exposure rate, and the exponentiated γ_i are the estimated RRs of the modifying factors relative to the baseline ERR.

Subsequent models were fit, whereby the five-year lagged total cumulative radon exposure (in WLM) was portioned into temporal exposure windows with $w_{5\text{-}14}$, $w_{15\text{-}24}$ and w_{25+} defining the exposures incurred 5–14 years, 15–24 years, and 25+ years before the attained age, such that:

$$\boldsymbol{Rate_w = Rate_0 \times [1.0 + \beta\, (w_{5-14} + \theta_{15-24} w_{15-24} + \theta_{25+} w_{25+})\, exp\, (\textstyle\sum_i \gamma_i\, z_i)]} \quad \textbf{(3)}$$

The $\theta_{15\text{-}24}$ and θ_{25+} represent the contributions to risk from 15−24 years and 25 + years before the attained age, relative to the 5–14 year window. Here, effect modifying factors z_i, represent categories of attained age (four categories: < 55, 55−64, 65−74, 75 + years)

and exposure rate (three or six categories: < 0.5, 0.5−4.9, 5.0 + WL; < 0.5, 0.5−1.0, 1.0−3.0, 3.0−5.0, 5.0−15, 15 + WL) (National Research Council 1999).

Calendar year period at risk, which was a background stratification factor in the primary analyses, is closely associated with many other variables of interest, such as exposure rate, duration of exposure, time since exposure (Lubin, Boice et al. 1994), and especially the accuracy of measurements of radon exposure. Thus, the background lung cancer mortality rate was only stratified by sub-cohort and age at risk in the effect modifier analysis.

Similar to the < 100 WLM restricted analysis, a sensitivity analysis restricting the effect modifier analysis on exposure rate (≤ 5.0 WL) was conducted. This includes all person-years, deaths, cumulative exposures (5-year lagged), and other time-dependent covariates (age at risk, calendar year period at risk, etc.) that occurred up to the ≤ 5.0 WL cut point. This includes information from all workers up to this cut point, even if their exposure rates are > 5 WL. All information that occurred at exposure rates > 5 WL was excluded. The sensitivity analysis (≤ 5.0 WL) includes 616 lung cancer deaths and 419,521 person-years of follow-up.

5.5.5 Statistical software

All statistical analyses were carried out using the AMFIT module in the EPIWIN implementation of EPICURE for Windows (Preston DL, Lubin JH, Pierce DA, McConney ME, Shilnikova NS. 2002), Version 1.0.0 (last updated 13/05/2002). EPICURE has been designed specifically for radiation research (Preston, Lubin et al. 2015).

The AMFIT program is a Poisson regression program designed for grouped cohort survival data research (Preston, Lubin et al. 2015). Data on individual members of the cohort have been cross-classified on one or more time scales and other factors. The basic data in each cell of this cross-classification are total time at risk (person-years) and number of deaths.

Person-year tables were prepared using the DATAB module in the EPICURE software package. Dr. Lydia Zablotska prepared the Beaverlodge person-year tables, and Dr. Ladislav Tomášek prepared the French and Czech person-year tables in preparation for this dissertation.

Tests of statistical significance use the likelihood ratio test, comparing two nested models with and without the cumulative radon exposure variable. All *P* values were two sided, and 95% confidence limits were reported. Possible values of β from the ERR models were limited by the requirement that the corresponding RR estimate could not be negative (Zablotska, Lane et al. 2013).

5.6 Sensitivity Analysis of the Confounding Effect of Unmeasured Tobacco Smoking

No information on tobacco smoking was available in the primary dataset being analyzed (the joint cohort study). So, two different sensitivity analyses of the unmeasured confounder were devised to quantify its potential impact on the radon-lung cancer estimates from the primary analyses. External data on the strength of association of the tobacco-lung cancer mortality relationship, the prevalence of tobacco smoking across exposure categories, and information on smoking-unadjusted and smoking-adjusted risk estimates were required.

The first method used a model for exposure and smoking effects to estimate bias due to smoking, relying on external information of the prevalence of tobacco smoking across categories of radon exposure in miners and the strength of association of tobacco smoking on lung cancer in a reference population. This analysis used the relative risk model, and for simplification, the 50–99 WLM (exposed) category was compared to < 25 WLM (reference) category. The second method used unadjusted RR and adjusted RR estimates at 100 WLM from nested case-control studies to estimate the magnitude of bias due to smoking.

5.6.1 Method 1: A model for exposure and smoking effects using external sources of data on smoking prevalence in exposed and reference miners, and for strength of association

A sensitivity analysis method of adjusting for an unmeasured confounder was first introduced by Cornfield and colleagues in 1959 (Cornfield, Haenszel et al. 1959), and later refined (Schlesselman 1978, Bross 1967, Axelson 1978). A modified version of these methods was applied to the joint cohort analysis, as described in Steenland and Greenland (2004).

5.6.1.1 External data on the strength of association between tobacco smoking and lung cancer

Gandini and colleagues found the pooled relative risk of lung cancer for current and former smokers, compared to never smokers, was RR = 8.96 (95% CI: 6.73–12.11) and RR = 3.85 (95% CI: 2.77–5.34), respectively. This information was the result of a systematic meta-analysis of 254 observational studies on cigarette smoking and 13 cancer sites from 1961 to 2003 (177 case-controls studies, 75 cohort studies and two nested case-control studies) (Gandini, Botteri et al. 2008). For lung cancer, dose-response estimates were available in 44 studies: 19 with estimates only for men, 11 with estimates only for women and 14 with separate estimates for men and for women. Studies on lung cancer included incidence and mortality as outcomes; studies of different sexes, ethnic groups, and countries, and studies of the general population and occupational groups. This meta-analysis is the most comprehensive source of information currently available on the strength of association of tobacco smoking on lung cancer. The risk estimates from this meta-analysis were adopted by the most recent IARC Monograph on Tobacco (IARC 2012a).

5.6.1.2 External data on the prevalence of tobacco smoking

Ideally, information on the prevalence of tobacco smoking among different categories of exposure in miners would come from a population with similar characteristics as the historical miners in the three cohorts under study. Information on tobacco smoking was obtained from a combined case-control analysis nested within French, Czech, and German cohorts (Hunter, Muirhead et al. 2013), because this offered the greatest overlap with the workers of the three cohorts in the present analyses. This study included uranium miners; 1046 cases and 2492 controls. Five, three, and two controls per lung cancer death were chosen from the updated French, Czech, and German cohort studies, respectively. Controls were selected from miners who were alive in the country specific cohort without lung cancer at the time of the corresponding lung cancer death. They were matched to the case in the same cohort by period of birth and attained age (still alive at the time of death of the case – the index date). Smoking information from company medical files or self-administered questionnaires (in person, relatives) was categorized into three levels: never smoker, long term ex-smoker (those who had quit smoking more than 10 years before the index year), and ex-smokers who had quit smoking less than 10 years before the index year together with current smokers.

The author, Dr. Nezahat Hunter, was contacted to request data on the prevalence of tobacco smoking, stratified by radon-exposure categories, among the control series, to reflect smoking distribution in the source population of the cohort of miners restricted to < 300 WLM (Hunter, Muirhead et al. 2013). This information is provided in Table 5-8.

A 1993 cohort of Ontario uranium miners (Kusiak, Ritchie et al. 1993) found that 80% of uranium miners with < 40 WLM exposure and 82% of those with ≥ 40 WLM were ever

smokers. Finally, a smoking survey of modern Saskatchewan uranium miners (CNSC 2003) indicated that approximately 70% of miners smoked. These studies indicated that a range of potential tobacco smoking prevalence, 60–80%, among uranium miners was reasonable.

Table 5-8 Prevalence of tobacco smoking among controls, by cumulative radon exposure categories, for the < 300 restricted analysis European joint nested case-control study (Dr. Nezahat Hunter, special tabulations, 2016-10-17)

Cumulative radon exposure (WLM)	Never smokers N (%)	Ex ≥ 10 years N (%)	Current and Ex < 10 years N (%)	Total
< 25 WLM	149 (20.4%)	195 (26.7%)	385 (52.8%)	**729**
25–49 WLM	71 (31.1%)	60 (26.3%)	97 (42.5%)	**228**
50–99 WLM	136 (30.9%)	89 (20.2%)	215 (48.9%)	**440**
Total	**356 (25.5%)**	**344 (24.6%)**	**697 (49.9%)**	**1397**

Table only provides smoking tabulations for categories less than 100 WLM.
Tobacco smoking prevalence reflects the distribution in controls only.

5.6.1.3 Method of analysis

The confounding effect is derived by hypothesizing patterns of smoking across categories of radon exposure, and estimating the effect of smoking in the absence of a radon effect. The magnitude of confounding bias was estimated when comparing cumulative radon exposure 50–99 WLM to a reference group with < 25 WLM cumulative radon exposure.

A simplifying assumption was made such that the effect of radon is constant across levels of smoking. If $p_{(\text{never, 50–99 WLM})}$, $p_{(\text{former, 50–99 WLM})}$, $p_{(\text{current, 50–99 WLM})}$ and $p_{(\text{never, < 25 WLM})}$, $p_{(\text{former, < 25 WLM})}$, $p_{(\text{current, < 25 WLM})}$ are the proportions of never, former and current smokers in the two categories of exposure, then the elevation in the rate of lung cancer mortality due to smoking in the reference group (radon < 25 WLM) would be a weighted average of the smoking-specific rate ratios,

$$\boldsymbol{RR_{<25\,WLM}} = \boldsymbol{p_{(never,<25\,WLM)}} + \boldsymbol{exp}\,(\boldsymbol{\beta_2})\,\boldsymbol{p_{(former,<25\,WLM)}} + \boldsymbol{exp}\,(\boldsymbol{\beta_3})\,\boldsymbol{p_{(current,<25\,WLM)}}$$

And the elevation in the rate of lung cancer mortality in exposed group (50–99 WLM) due to smoking would be a weighted average of the same rate ratios but with different weights.

$$\boldsymbol{RR_{50\text{–}99\,WLM}} = \boldsymbol{p_{(never,50\text{–}99\,WLM)}} + \boldsymbol{exp}\,(\boldsymbol{\beta_2})\,\boldsymbol{p_{(former,50\text{–}99\,WLM)}} + \boldsymbol{exp}\,(\boldsymbol{\beta_3})\,\boldsymbol{p_{(current,50\text{–}99\,WLM)}}$$

Assuming no other unmeasured confounders and assuming that radon exposure has no effect on the risk of lung cancer mortality, the magnitude of bias due to confounding by smoking status in the comparison of 50–99 WLM radon exposure to < 25 WLM reference radon exposure would be derived by $RR_{50–99\ WLM}$ / $RR_{<25\ WLM}$.

$$\mathbf{B}ias = \frac{RR_{50-99\,WLM}}{RR_{<25\,WLM}} = \frac{p_{never,50-99\,WLM} + exp\,(\beta_2)\,p_{former,50-99\,WLM} + exp\,(\beta_3)\,p_{current,50-99\,WLM}}{p_{never,<25\,WLM} + exp\,(\beta_2)\,p_{former,<25\,WLM} + exp\,(\beta_3)\,p_{current,<25\,WLM}} \quad \textbf{(4)}$$

This bias can then be applied to the observed (smoking unadjusted) estimate to generate a smoking-adjusted RR for radon. The smoking-unadjusted RR derived in the primary analyses from our joint cohort data is divided by the bias factor estimated above:

$$RR_{adj} = \frac{RR_{unadj}}{Bias} \quad \textbf{(5)}$$

Figure 3 illustrates this derivation of bias using smoking prevalence estimates from Table 5-8 and the relative risk of lung cancer for current and former smokers compared to never smokers from a meta-analysis (Gandini, Botteri et al. 2008). The resulting bias estimate was 0.916.

The prevalence of ever tobacco smoking was also varied from 60% to 80% for 30 different scenarios for this multi-dimensional sensitivity analysis. The range of prevalence reflects the prevalence of tobacco smoking in the Ontario uranium miners (80%) cohort (Kusiak, Ritchie et al. 1993), modern Saskatchewan uranium miners (70%) in Canada (CNSC 2003) and potential reductions in future smoking prevalence (60%) in uranium miners.

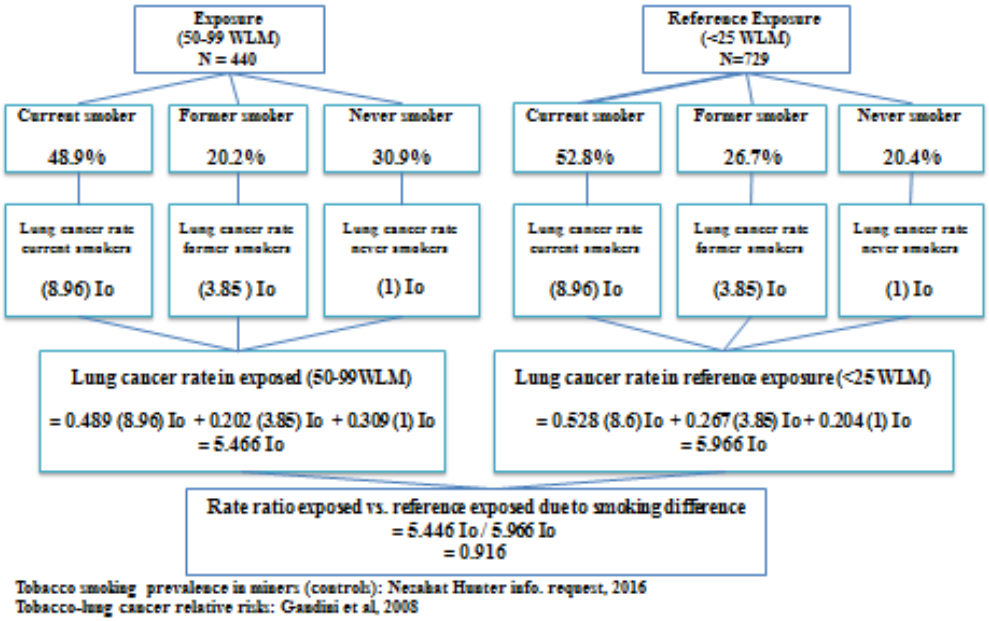

Figure 3 Example of confounding of the radon-lung cancer relationship by tobacco smoking, assuming no effect of radon exposure on lung cancer, in the European joint nested case-control study of uranium miners restricted to < 300 WLM, controls only

5.6.2 Method 2: A model for exposure and smoking effects using unadjusted RR and adjusted RR from nested case-control studies

An alternative method for deriving the bias factor due to unmeasured smoking was based on the use of smoking-unadjusted and smoking-adjusted relative risks at 100 WLM that were available in nested case-control studies of uranium miners, as listed in Table 5-9 (Leuraud, Billon et al. 2007, Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013, Tomasek 2011, Tomasek 2013, Schnelzer, Hammer et al. 2010, L'Abbé, Howe et al. 1991).

Table 5-9 Smoking unadjusted and smoking adjusted relative risks at 100 WLM and bias ratio for French, Czech, German and Beaverlodge case-control studies

Nested case control study	Smoking-unadjusted RR at 100 WLM	Smoking-adjusted RR at 100WLM	Bias factor
Leuraud et al, 2011 (CZ, FR, GR)	2.00	1.80	1.11
Leuraud et al, 2011 (CZ1953–, FR & GR 1956–) (late sample)	2.70	2.50	1.08
Hunter et al, 2013 (< 300 WLM) (CZ, FR, GR)	3.30	2.70	1.22
Hunter et al, 2013 (< 100 WLM) (CZ, FR, GR)	4.90	4.70	1.04
Tomášek et al, 2011 (CZ)	2.80	2.50	1.12
Tomášek et al, 2013 (CZ)	2.40	2.30	1.04
Leuraud et al, 2007 (FR)	1.98	1.85	1.07
Schnelzer et al, 2010 (GR)	1.25	1.23	1.02
L'Abbé et al, 1991 (BL)	4.89	4.93	0.99

Cumulative radon exposures (WLM) were lagged five years.
Nested case-control studies were matched on cohort, attained age and age at birth.
CZ: Czech; FR: French; GR: German; BL: Beaverlodge.
The bias factor due to smoking difference in each nested case-control study equals the $RR_{unadjusted}$ / $RR_{adjusted}$ at 100 WLM within the specific nested case-control study.

The bias factor due to smoking was calculated by dividing the smoking-unadjusted RR at 100 WLM within the nested case-control study, by the smoking-adjusted RR at 100WLM. A range of smoking-adjusted RR at 100 WLM for radon in the primary dataset were then estimated by dividing the smoking-unadjusted RR at 100 WLM in the primary joint cohort analysis by each bias factor, in turn.

6 Results

6.1 Demographic and Exposure Characteristics of the Cohorts

A total of 649 lung cancer deaths and 428,356 person-years at risk were observed when the three cohorts' mortality updates ended in 1999 (Table 6-1). This included 389 deaths from lung cancer that occurred during 196,533 person-years of observation in Czech miners, during the period 1953–1999; 65 lung cancer deaths in 80,859 person-years of observation in French miners (1956–1999); and 195 lung cancer deaths in 150,965 person-years of observation in Beaverlodge miners (1965–1999).

Table 6-1 also presents the distribution of cumulative occupational radon exposures. The three cohorts had very different mean and maximum cumulative exposures. The Beaverlodge cohort had the highest cumulative radon exposures (mean = 118.5 WLM, max. = 1,617.0); the French cohort had the lowest (mean = 36.4, max. = 127.7).

Table 6-1 Basic characteristics of the Czech (1953−1999), French (1956−1999), and Beaverlodge (1965−1999) cohorts

Cohort	Lung cancer deaths	%	Person-years	%	Cumulative radon exposures (WLM)		
					Mean	Std. Dev.	Max.
Czech	389	59.9	196,533	45.9	95.5	75.4	363.0
French	65	10.0	80,859	18.9	36.4	32.0	127.7
Beaverlodge	195	30.0	150,964	35.2	118.5	195.8	1,617.0
Combined	**649**	**100.0**	**428,356**	**100.0**	**95.5**	**144.3**	**1,617.0**

Czech 1953−1999 cohort; French 1956−1999 cohort; Beaverlodge 1965−1999 cohort.
This does not represent individuals, but grouped data. Cumulative radon exposure (five-year lagged, WLM), weighted by person-years at risk.
The person-years for France were corrected to adjust for 32% missing causes of death in France before 1965, and 28% missing causes of death from 1965−1969 (thus 80,859.3 person-years). France had 86,038.3 person-years of follow-up if missing causes of death were not adjusted for.
Abbreviations used: WLM: working level month.

The distribution of person-years at risk by age at risk, calendar year period at risk and cumulative radon exposure is presented in Table 6-2. Over half (54.9%) of the person-

years at risk were accumulated before age 45 years. The great majority (92.0%) of the person-years were accumulated at < 100 WLM cumulative radon exposures, and this is the study base for the primary analysis. A substantial proportion of person-years (62.2%) occurred at cumulative radon exposures < 10 WLM.

The distribution of lung cancer deaths, person-years at risk and crude mortality rates are presented in Table 6-3. The crude lung cancer mortality rate increased steadily with attained age up to age 74 years. Lung cancer mortality increased steadily with increasing cumulative radon exposure, up to about 200 WLM.

Table 6-2 Distribution of person-years at risk by age at risk, calendar year period at risk, cumulative radon exposure and cohort

	Person-years								
	Czech	**%**	**French**	**%**	**Beaverlodge**	**%**	**Combined**	**%**	**Cum %**
Age at risk									
< 39	91,923	46.8	35,077	43.4	41,365	27.4	**168,365**	**39.3**	**39.3**
40−44	32,190	16.4	12,223	15.1	22,415	14.8	**66,828**	**15.6**	**54.9**
45−49	28,669	14.6	9,666	12.0	21,459	14.2	**59,793**	**14.0**	**68.9**
50−54	17,071	8.7	7,637	9.4	19,416	12.9	**44,124**	**10.3**	**79.2**
55−59	10,854	5.5	6,208	7.7	16,427	10.9	**33,489**	**7.8**	**87.0**
60−64	7,738	3.9	4,740	5.9	13,158	8.7	**25,636**	**6.0**	**93.0**
65−69	4,785	2.4	3,015	3.7	8,589	5.7	**16,389**	**3.8**	**96.8**
70−74	2,157	1.1	1,469	1.8	4,493	3.0	**8,119**	**1.9**	**98.7**
75−100	1,146	0.6	824	1.0	3,642	2.4	**5,612**	**1.3**	**100.0**
Total	**196,533**	**100.0**	**80,859**	**100.0**	**150,964**	**100.0**	**428,356**	**100.0**	
Calendar year period at risk									
1955−1959	2,682	1.4	1,229	1.5	–	–	**3,911**	**0.9**	**0.9**
1960−1964	9,051	4.6	3,939	4.9	–	–	**12,990**	**3.0**	**3.9**
1965−1969	9,014	4.6	4,475	5.5	14,029	9.3	**27,518**	**6.4**	**10.4**
1970−1974	21,658	11.0	5,818	7.2	16,735	11.1	**44,210**	**10.3**	**20.7**
1975−1979	33,815	17.2	9,011	11.1	19,042	12.6	**61,867**	**14.4**	**35.1**
1980−1984	33,063	16.8	14,218	17.6	22,214	14.7	**69,495**	**16.2**	**51.4**
1985−1989	31,385	16.0	14,607	18.1	27,075	17.9	**73,067**	**17.1**	**68.4**
1990−1994	29,294	14.9	14,294	17.7	26,531	17.6	**70,118**	**16.4**	**84.8**
1995−1999	26,573	13.5	13,269	16.4	25,338	16.8	**65,180**	**15.2**	**100.0**
Total	**196,533**	**100.0**	**80,859**	**100.0**	**150,964**	**100.0**	**428,356**	**100.0**	
Cumulative radon exposure (WLM)									
0.0	28,360	14.4	25,384	31.4	18,711	12.4	**72,455**	**16.9**	**16.9**
> 0.0−4	86,751	44.1	30,520	37.7	49,581	32.8	**166,852**	**39.0**	**55.9**
5−9	9,574	4.9	1,607	2.0	15,842	10.5	**27,023**	**6.3**	**62.2**
10−19	18,820	9.6	8,270	10.2	17,354	11.5	**44,444**	**10.4**	**72.6**
20−39	11,375	5.8	7,202	8.9	16,337	10.8	**34,914**	**8.2**	**80.7**
40−59	10,633	5.4	3,291	4.1	7,233	4.8	**21,157**	**4.9**	**85.6**
60−79	7,652	3.9	2,495	3.1	6,999	4.6	**17,146**	**4.0**	**89.6**
80−99	6,673	3.4	1,516	1.9	2,055	1.4	**10,244**	**2.4**	**92.0**
100−149	10,165	5.2	573	0.7	8,238	5.5	**18,976**	**4.4**	**96.5**
150−199	4,108	2.1	0	0.0	1,926	1.3	**6,034**	**1.4**	**97.9**
200−249	1,834	0.9	0	0.0	3,195	2.1	**5,029**	**1.2**	**99.0**
250 +	589	0.3	0	0.0	3,492	2.3	**4,081**	**1.0**	**100.0**
Total	**196,533**	**100.0**	**80,859**	**100.0**	**150,964**	**100.0**	**428,356**	**100.0**	

Cumulative radon exposure (five-year lagged, WLM), weighted by person-years at risk.
The cumulative radon exposures > 100 WLM are shaded; these exposure levels are not the focus of this dissertation.
Abbreviations used: WLM: working level month.

Table 6-3 Lung cancer deaths, person-years at risk and mortality rate by age at risk, calendar year period at risk, and cumulative radon exposure for the joint cohort

	Lung cancer deaths	Person-years	Mortality rate (per 100,000)
Age at risk			
< 39	14	168,365	8.3
40−44	23	66,828	34.4
45−49	61	59,793	102.0
50−54	98	44,124	222.1
55−59	111	33,489	331.5
60−64	144	25,636	561.7
65−69	107	16,389	652.9
70−74	63	8,119	776.0
75 +	28	5,612	498.9
Total	**649**	**428,356**	**151.5**
Calendar year period at risk			
1955−1959	2	3,911	51.1
1960−1964	18	12,990	138.6
1965−1969	48	27,518	174.4
1970−1974	62	44,210	140.2
1975−1979	73	61,867	118.0
1980−1984	107	69,495	154.0
1985−1989	98	73,067	134.1
1990−1994	119	70,118	169.7
1995−1999	122	65,180	187.2
Total	**649**	**428,356**	**151.5**
Cumulative radon exposure (WLM)			
0.0	32	72,455	44.2
> 0.0−4	71	166,852	42.6
5−9	19	27,023	70.3
10−19	48	44,444	108.0
20−39	63	34,915	180.4
40−59	66	21,157	312.0
60−79	64	17,147	373.2
80−99	45	10,244	439.3
100−149	101	18,976	532.2
150−199	63	6,035	1044.0
200−249	43	5,029	855.1
250 +	34	4,081	833.1
Total	**649**	**428,356**	**151.5**

Czech 1953−1999 cohort; French 1956−1999 cohort; Beaverlodge 1965−1999 cohort.
Cumulative radon exposure (five-year lagged, WLM), weighted by person-years at risk.
The cumulative radon exposures > 100 WLM are shaded; these exposures levels are not the focus of this dissertation.
Abbreviations used: WLM: working level month.

6.2 Continuous Linear Dose Response Analysis of Radon Exposure-Associated Lung Cancer Mortality Rates

Table 6-4 presents the Poisson regression excess relative risks per working level month (ERR/WLM) of lung cancer mortality by mean cumulative radon exposure for the joint cohort. The results reflect background stratification for sub-cohort (3 levels), age at risk (12 levels), and calendar year period at risk (9 levels).

The risk of lung cancer mortality increased continuously with increasing cumulative radon exposure among uranium miners. The ERR/WLM analysis was first restricted to workers with < 100 WLM cumulative radon exposures, which represented 408 lung cancer deaths and 394,236 person-years at risk. The linear excess relative risk model was statistically significant. The ERR/WLM was 0.017 (95% CI: 0.009−0.028; $P < 0.001$). Next, the ERR/WLM analysis was restricted to workers with cumulative radon exposures < 50 WLM. The relationship between cumulative radon exposures and lung cancer mortality was again statistically significant. The ERR/WLM was 0.023 (95% CI: 0.008−0.043; $P < 0.001$). The ERR/WLMs were greater when estimated using restricted person-year strata for the lower cumulative exposure ranges (< 50WLM and < 100 WLM) compared to the full cumulative exposure range (0–1,617 WLM).

Table 6-5 presents the ERR/WLM of lung cancer mortality by mean cumulative radon exposure and cohort. The results reflect models with background rate stratification on age at risk and calendar year period at risk.

The relationship between cumulative radon exposures and lung cancer mortality was highly statistically significant at < 100 WLM cumulative radon exposures. The risk

estimates ranged from an ERR/WLM = 0.011 (95% CI: 0.002−0.026; P = 0.008) for the Czech cohort and 0.022 (95% CI: 0.005−0.055; P = 0.005) and 0.021 (95% CI: 0.008−0.044; P < 0.001) for the French and Beaverlodge cohorts, respectively.

Table 6-4 Excess relative risks of lung cancer mortality by mean cumulative radon exposure for the joint cohort

Cumulative radon exposure	Strata	Lung cancer deaths	Person-years	Mean cumulative exposure (WLM)	ERR/WLM[a] (MLE)	95% CI[c]	*P* Value (parameter)	LR statistic	*P* Value (LR[b])
< 100 WLM	sub-cohort, age, year	408	394,236	36.42	0.017	0.009−0.028	< 0.001	26.6	< 0.001
< 50 WLM	sub-cohort, age, year	276	360,370	20.35	0.023	0.008−0.043	0.008	12.67	< 0.001
0–1,617 WLM	sub-cohort, age, year	649	428,356	95.49	0.014	0.010−0.020	< 0.001	129.7	< 0.001

[a] Poisson regression model, for grouped survival data, with background stratification on sub-cohort, age at risk and calendar year period at risk.
[b] *P* values from the likelihood ratio test comparing models with and without exposure variable.
[c] Likelihood bounds for exposure variable (WLM).
Cumulative radon exposure (five-year lagged, WLM), weighted by person-years at risk.
Abbreviations used: WLM, working level months; ERR/WLM, excess relative risk per working level month; CI confidence interval; LR, likelihood ratio, MLE, maximum likelihood estimate.

Table 6-5 Excess relative risks of lung cancer mortality by mean cumulative radon exposure and cohort

Cumulative radon exposure	Cohort	Strata[a]	Lung cancer deaths	Person-years	Mean cumulative exposure (WLM)	ERR/WLM[a] (MLE)	95% CI[c]	LR statistic	*P* Value (LR[b])
< 100 WLM	Czech	age (12), year (9)	223	179,837	45.1	0.011	0.002−0.026	7.1	0.008
	French	age (12), year (9)	62	80,286	32.9	0.022	0.005−0.055	8.0	0.005
	Beaverlodge	age (13), year (7)	123	134,113	32.3	0.021	0.008−0.044	12.6	< 0.001
< 50 WLM	Czech	age (12), year (9)	133	161,226	24.5	0.013	- 0.003−0.046	2.3	0.133
	French	age (12), year (9)	43	74,898	18.0	0.018	- 0.009−0.075	1.3	0.262
	Beaverlodge	age (13), year (7)	100	124,247	19.5	0.032	0.010−0.071	10.2	0.001
0–1,617 WLM	Czech	age (12), year (9)	389	196,533	95.5	0.021	0.012−0.035	76.7	< 0.001
	French	age (12), year (9)	65	80,859	36.4	0.022	0.005−0.053	9.4	0.002
	Beaverlodge	age (13), year (7)	195	150,964	118.5	0.009	0.005−0.015	49.0	< 0.001

Poisson regression model, for grouped survival data, with background stratification on age at risk and calendar year period at risk.
[a] The Beaverlodge cohort was stratified age at risk (13 categories), calendar year period at risk (7 categories); the Czech and French cohorts were stratified for age at risk (12 categories), and calendar year period t risk (9 categories).
[b] *P* values from the likelihood ratio test comparing models with and without exposure variable.
[c] Likelihood bounds for exposure variable (WLM).
Cumulative radon exposure (five-year lagged, WLM), weighted by person-years at risk.
Abbreviations used: WLM, working level months; ERR/WLM, excess relative risk per WLM; CI confidence interval; LR, likelihood ratio.

6.2.1 Sensitivity analysis of Beaverlodge prevalent hires

There was minimal difference in the ERR/WLMs between the two calendar time periods (1950–1999, 1965–1999), for the whole range of cumulative radon exposures for the Beaverlodge cohort, with at least six months employment, or for the restricted analysis < 100 WLM.

Table 6-6 Excess relative risk of lung cancer mortality by calendar year at risk and mean cumulative radon exposure, Beaverlodge cohort, 6 months+ duration of employment

Calendar year period at risk	Cumulative exposure range (WLM)	Lung cancer deaths	Person-years	Mean cumulative exposure (WLM)	ERR/WLM (MLE)	95% CI	LR statistic[b]	*P* value (LR)[a]
1950–1999	0–100	126	142,673	32.5	0.0212	0.008–0.043	12.9	< 0.001
	0–2,453	201	161,958	123.5	0.0091	0.005–0.015	51.13	< 0.001
1965–1999	0–100	123	134,113	32.3	0.0215	0.008–0.044	12.6	< 0.001
	0–1,617	195	150,964	118.5	0.0091	0.005–0.015	48.95	< 0.001

Poisson regression model, for grouped survival data, with background stratification on age at risk and calendar year period at risk.
The Beaverlodge cohort was stratified age at risk (13 categories), calendar year period at risk (7 categories).
[a] *P* values from the likelihood ratio test comparing models with and without exposure variable.
[b] Likelihood bounds for exposure variable (WLM).
Cumulative radon exposure (five-year lagged, WLM), weighted by person-years at risk.
Abbreviations used: WLM, working level months; ERR/WLM, excess relative risk per WLM; CI confidence interval; LR, likelihood ratio.

In the second sensitivity analysis (not shown), the total Beaverlodge cohort (1950–1999) had 279 lung cancer deaths and 285,846 person-years (refer to Table 5-2), and ERR/WLM = 0.0092. The restricted Beaverlodge cohort for this dissertation (1965–1999) had 269 lung cancer deaths and 248,580 person-years, and ERR/WLM = 0.0091. Finally, the restricted Beaverlodge cohort with non-zero radon exposures before 1965, had 175 lung cancer deaths and 162,718 person-years, and ERR/WLM = 0.0088.

6.3 Categorical Exposure-Response Analysis (RR) of < 100 WLM Cumulative Radon Exposure Associated Lung Cancer Mortality Risks

Table 6-7 and Figure 4 presents results for the risk ratios for the categorical exposure-response of cumulative WLM. This Poisson regression analysis includes 408 lung cancer deaths and 394,236 person-years at risk in the joint cohort of workers with < 100 WLM cumulative radon exposures. A monotonic increase in estimates was observed, with a statistically significant estimate seen at mean cumulative radon exposures of approximately of 15 WLM (RR = 1.64; 95% CI: 1.03−2.65).

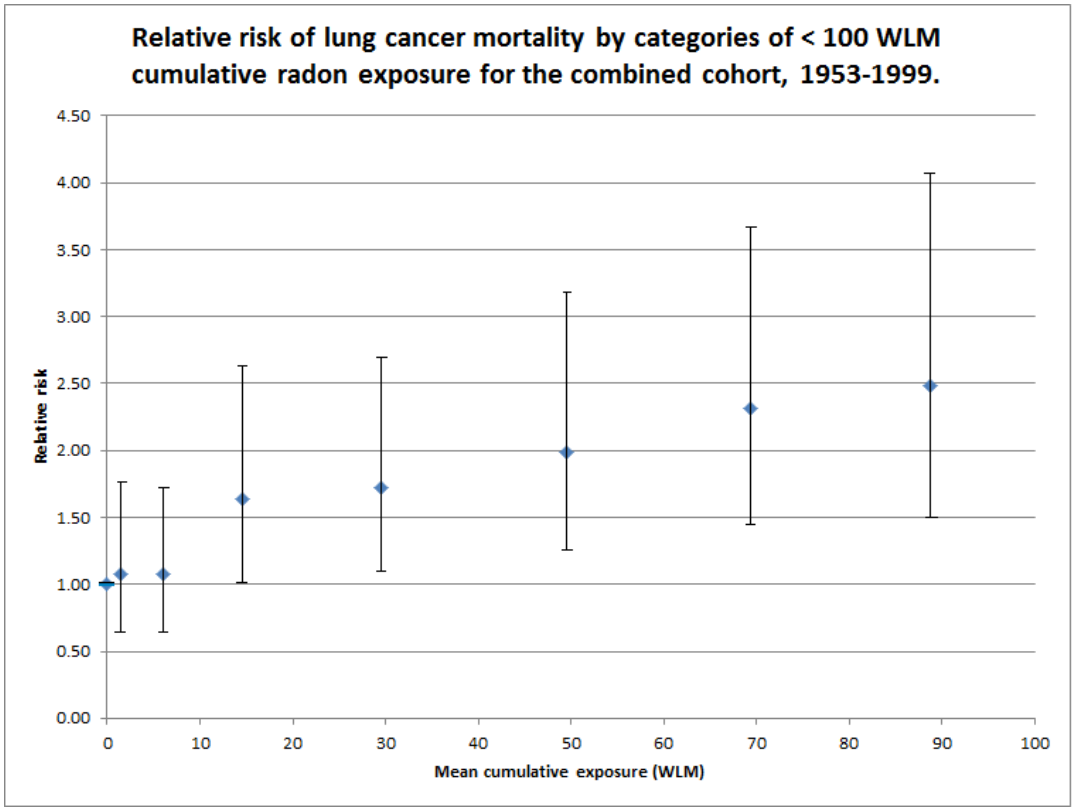

Figure 4 Relative risk of lung cancer mortality by categories of < 100 WLM cumulative radon exposure for the joint cohort, 1953–1999

Table 6-8 presents estimated RR for each cohort separately. Analyses were conducted using similar cumulative exposure categories as the joint analysis; however, some categories were joint because of few lung cancer deaths (i.e. < five) within the exposure category.

The French and Beaverlodge cohorts had statistically significant (P = 0.007, P = 0.009) increased risk of lung cancer death with increased cumulative radon exposure. The Czech cohort did not (P = 0.157) even though RRs increased with increasing cumulative exposure.

In the Beaverlodge cohort, a statistically significant increase in risk was first seen at mean cumulative exposures around 15 WLM (RR = 2.15; 95% CI: 1.04−4.52). A statistically significantly three-fold increase in risk of lung cancer death (RR = 3.10; 95% CI: 1.57−6.32) was found in the highest exposure category (60−100 WLM) compared to the lowest exposure category. In the Czech and French cohorts, a statistically non-significant increased risk of lung cancer death was found in the highest exposure categories (RR = 1.98; 95% CI: 0.74−6.56) and (RR = 2.12; 95% CI: 0.99−4.67), respectively.

Table 6-7 Relative risks of lung cancer mortality by categories of < 100 WLM cumulative radon exposure for the joint cohort

Cumulative radon exposure (WLM)	Mean cumulative exposure (WLM)	Lung cancer deaths	%	Person-years	%	Relative Risk (MLE)	95% CI	LR statistic	Degrees of freedom	*P* Value
0.0	0.0	32	7.8	72,455	18.4	1.00		30.88	7	< 0.001
> 0.0−2	1.5	39	9.6	109,620	27.8	1.08	0.66–1.79			
3−9	6.0	51	12.5	84,256	21.4	1.08	0.67–1.74			
10−19	14.6	48	11.8	44,444	11.3	1.64	1.03–2.65			
20−39	29.6	63	15.4	34,915	8.9	1.72	1.11–2.72			
40−59	49.5	66	16.2	21,157	5.4	1.99	1.27–3.20			
60−79	69.4	64	15.7	17,147	4.3	2.31	1.47–3.70			
80−100	88.7	45	11.0	10,244	2.6	2.48	1.52–4.09			
Total		**408**	**100.0**	**394,236**	**100.0**					

Deviance 2412.437

Abbreviations used: WLM, working level months; CI confidence interval; MLE: Maximum likelihood estimate; LR: Likelihood ratio.

Relative risks were stratified by sub-cohort (3 categories), age at risk (12 categories), and calendar year period at risk (9 categories).

P value of the test of linear trend based is on mean values for exposure categories.

Workers with zero cumulative radon exposures are included in the 0.0 WLM category; workers who had cumulative exposures ranging from 0.010−2.999 WLM are included in the > 0.0−2 WLM category.

Table 6-8 Relative risks of lung cancer mortality by categories of < 100 WLM cumulative radon exposure by cohort

Cumulative radon exposure (WLM)	Mean cumulative exposure (WLM)	Lung cancer deaths	%	Person-years	%	Relative Risk (MLE)	95% CI	LR statistic	Degrees of freedom	*P* Value
Czech										
0.0	0.0	5	2.2	28,360	15.8	1.00		10.6	7	0.157
> 0.0−2	2.2	17	7.6	52,242	29.0	0.88	0.30–3.11			
3−9	5.8	28	12.6	44,083	24.5	0.85	0.31–2.84			
10−19	14.6	25	11.2	18,820	10.5	1.33	0.49–4.45			
20−39	29.4	31	13.9	11,375	6.3	1.34	0.51–4.45			
40−59	50.1	46	20.6	10,633	5.9	1.46	0.56–4.79			
60−79	69.6	36	16.1	7,652	4.3	1.50	0.56–4.98			
80−100	88.9	35	15.7	6,673	3.7	1.98	0.74–6.56			
TOTAL		**223**	**100.0**	**179,837**	**100.0**					
French										
0.0	0.0	13	21.0	25,384	31.6	1.00		14.2	4	0.007
> 0.0−9	3.3	13	21.0	32,127	40.0	0.51	0.23–1.14			
10−19	14.9	6	9.7	8,270	10.3	1.09	0.37–2.82			
20−59	38.3	13	21.0	10,493	13.1	1.11	0.50–2.47			
60−100	77.6	17	27.4	4,012	5.0	2.12	0.99–4.67			
TOTAL		**62**	**100.0**	**80,286**	**100.0**					
Beaverlodge										
0.0	0.0	14	11.4	18,369	13.7	1.00		17.0	6	0.009
> 0.0−2	1.4	20	16.3	44,571	33.2	1.82	0.91–3.76			
3−9	6.4	12	9.8	21,194	15.8	1.68	0.75–3.71			
10−19	14.5	17	13.8	17,354	12.9	2.15	1.04–4.52			
20−39	29.8	23	18.7	16,337	12.2	2.12	1.09–4.30			
40−59	48.7	16	13.0	7,233	5.4	3.68	1.77–7.78			
60−100	77.0	21	17.1	9,054	6.8	3.10	1.57–6.32			
TOTAL		**123**	**100.0**	**134,113**	**100.0**					

Deviance: Czech 1223.165, French 419.809; Beaverlodge 757.227
Abbreviations used: WLM, working level months; CI confidence interval; MLE: Maximum likelihood estimate; LR: Likelihood ratio
P value of the test of linear trend using mean values for exposure categories. Cumulative radon exposures were lagged five years.
Relative Risks for the Czech and French cohorts were stratified by age at risk (12 categories) and calendar year period at risk (9 categories).
Relative Risks for the Beaverlodge cohort were stratified by age at risk (13 categories) and calendar year period at risk (7 categories).
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6.4 Effect Modifiers

Table 6-9 presents the distribution of effect modifiers for the three cohorts. Attained age, age at first exposure and time since first exposure were similar for Czech and French cohorts. The mean attained age was 53 years (range 18−83), the mean age at first exposure was 29 years (range 13−62), and the mean time since first exposure was 24 years (range 0−47). Attained age was provided only as a categorical variable for the Beaverlodge cohort. Czech and Beaverlodge miners had considerably higher cumulative radon exposures than French miners for each time since exposure window. Beaverlodge miners had the highest exposure rates, with a mean exposure rate of 2.64 WL, compared to 1.02 WL and 0.27 WL for the Czech and French miners, respectively.

Table 6-9 Distribution of effect modifier variables by cohort

Variable	Cohort	Mean	Std. Dev.	Range
Attained age	Czech	53.32	10.81	19−83
	French	53.42	10.96	18−82
Age at first exposure	Czech	29.51	9.95	13−62
	French	29.23	8.579	15− 7
Time since first exposure	Czech	24.20	8.12	0−47
	French	24.65	9.61	0−44
Cumulative radon exposure (WLM) 5−14 years	Czech	24.23	40.90	0−327.7
	French	11.62	15.17	0−75.72
	Beaverlodge	21.73	73.65	0−1,468
Cumulative radon exposure (WLM) 15−24 years	Czech	43.23	50.63	0−302.3
	French	15.57	17.33	0−76.08
	Beaverlodge	53.31	123.41	0−1,531
Cumulative radon exposure (WLM) 25+ years	Czech	28.0	49.26	0−363
	French	9.20	15.86	0−95.78
	Beaverlodge	43.47	124.95	0−1,531
Exposure rate (WL)	Czech	1.02	0.77	0−5.1
	French	0.27	0.23	0−7.04
	Beaverlodge	2.64	4.02	0−29.44

WLM, working level months; WL, working level.
Exposure rate (WL) = cum. exposure (WLM)/duration of exposure (months).

6.4.1 < 100 WLM cumulative radon exposures

Table 6-10 illustrates the excess relative risk of lung cancer per 100 WLM considering the modifying effects of time since exposure, attained age and exposure rate.

In Model A, the ERR/WLM = 0.022 (95% CI: 0.013−0.034, $P < 0.001$) corresponds to the lung cancer excess relative risk when radon exposure was stratified by sub-cohort and age at risk, prior to any consideration of effect modifiers. The estimate differs from that reported in Table 6-4, because calendar year period at risk was not included in the background stratification to avoid collinearity with time since exposure; thus the ERR/WLM is 0.022 instead of 0.017.

In Model B, the excess relative risk of lung cancer mortality decreased significantly with increasing time since exposure. The estimate, 0.035 (95% CI: 0.018−0.060) corresponds to the ERR/WLM for exposures received 5−14 years previously. The ERR/WLM of exposures received more than 25 years previously resulted in an ERR 0.33 times that of the exposure effect in the 5−14 window; that is, compared to the ERR in the 5−14 window, the ERR/WLM for exposures in the 25+ window would be 0.035*0.33 = 0.012; 95% CI: 0.004−0.023).

In Model C, the addition of attained age resulted in a lung cancer risk of ERR/WLM = 0.047; 95% CI: 0.020−0.096, for miners aged < 55 years with exposures received 5−14 years previously. Multiplying the remaining time since exposure or attained age parameter estimates by the lung cancer risk provided the risk for that time since exposure or attained age, respectively (as in Model B). The excess relative risk decreased with time since exposure. For attained age to age 75 years; however, the confidence interval was

very wide at age 75+ (95% CI: 0.00–3.24). Attained age was not an important effect modifier in the radon-lung cancer mortality relationship at < 100 WLM.

In Model D, the addition of exposure rate, for three exposure rate categories, resulted in a lung cancer risk of ERR/WLM = 0.056; 95% CI: 0.020−0.133 for miners with cumulative exposures received 5−14 years previously, attained age < 55 years, and exposure rate < 0.5 WL. However, confidence intervals were very wide, particularly among exposure rates 5.0 + WL due to few lung cancer deaths, or did not converge at all (i.e. age 75+).

Examining deviance statistics based on fitting the above models (refer to bottom of Table 6-10), only the addition of time since exposure windows as effect modifiers (Model B) led to a statistically significant improved in fit (LR *P* value = 0.002) over Model A. In contrast, adjusting for the modifying effects of attained age (LR *P* value = 0.448) (Model C) and exposure rate (Model D), even when varying the number of strata using either three or six categories (not shown) of exposure rate, did not lead to statistically significant improvements in fit (LR *P* value = 0.313, 0.430 respectively).

Table 6-10 Joint cohort restricted to < 100 WLM: excess relative risk and relative risk estimates of lung cancer mortality from the interaction models

Parameter	Deaths	Model A		Model B		Model C		Model D	
		Parameter estimate	95% CI	Parameter estimate	95% CI	Parameter estimate	95% CI	Parameter estimate	95% CI
Total WLM Exposure									
(β) ERR/WLM	408	0.022[a]	0.013−0.034	0.035[a]	0.018−0.060	0.047[a]	0.020−0.096	0.056[a]	0.020−0.133
Effect Modifiers				**Relative Risk**	**95% CI**	**Relative Risk**	**95% CI**	**Relative Risk**	**95% CI**
Time Since Exposure (WLM)									
5−14 years				1.00[b]		1.00[b]		1.00[b]	
15−24 years				0.96[b]	0.50−1.90	0.96[b]	0.50−1.86	0.89[b]	0.45−1.74
25+ years				0.33[b]	0.12−0.70	0.36[b]	0.11−0.76	0.38[b]	0.14−0.78
Attained Age (years)									
< 55	119					1.00[b]		1.00[b]	
55−64	167					0.82[b]	0.30−2.17	0.78[b]	0.29−2.10
65−74	99					0.37[b]	0.02−1.35	0.37[b]	0.04−1.26
75 +	23					0.26[b]	0.00−3.24	0.02[b]	N/A
Exposure Rate (WL)									
< 0.5	212							1.00[b]	
0.5−4.9	182							0.83[b]	0.48−1.66
5.0+	14							2.00[b]	0.44−5.86
Deviance		2,612.34		2,599.70		2,597.04		2,594.72	
Degrees of freedom		31,917		31,915		31,912		31,910	
Difference in deviance (LR statistic)				12.64		2.66		2.32	
Difference in degrees of freedom				2		3		2	
LR *P* value[c]				0.002		0.448		0.313	

[a] ERR/WLM for cumulative radon exposure, lagged five years.

[b] Relative risks for time since exposure, attained age, and exposure rate variables; stratification on sub-cohort (3 categories), and age at risk (12 categories). Parameters are estimated on the basis of the model below. Here the bracketed area represents the cumulative exposures and parameter estimates obtained in different time windows (5-14, 15-24, and 25+ years previously). Subscript $\boldsymbol{a}$ denotes categories of attained age and the subscript $\boldsymbol{z}$ denotes categories of radon concentration in WL.

$$\boldsymbol{Rate_w} = [\mathbf{1.0} + \boldsymbol{\beta}\,(\boldsymbol{w_{5-14}} + \boldsymbol{\theta_{15-24}}\boldsymbol{w_{15-24}} + \boldsymbol{\theta_{25+}}\boldsymbol{w_{25+}}) * \boldsymbol{\gamma_a}\,\boldsymbol{z_z}]$$

Abbreviations: WL, working levels; WLM, working level months; ERR/WLM, excess relative risk per working level months CI, confidence interval; LR, likelihood ratio; MLE, Maximum likelihood estimate; N/A, Not available due to convergence problem in the EPICURE package.

Maximum likelihood estimates and 95% confidence intervals.

[c] *P* value from a likelihood ratio test to assess the improvement in fit due to adding additional factors to the model.

As a sensitivity analysis, the effect modifier analysis was repeated leaving out one cohort at a time. In all three bi-cohort analyses, a statistically significant linear increased lung cancer risk with increasing radon exposure was found (Table 6-11) as the baseline risk, prior to assessing the effect modifiers (i.e., Model A).

Table 6-11 Bi-cohorts restricted to < 100 WLM: excess relative risk estimates of lung cancer mortality

Bi-cohort	Lung Cancer deaths	ERR/WLM	95% CI
Czech and Beaverlodge	346	0.022	0.011−0.034
Czech and French	285	0.021	0.010−0.033
French and Beaverlodge	185	0.022	0.009−0.036

ERR/WLM for total WLM exposure, lagged five years.
Abbreviations: WLM, working level months; ERR/WLM, excess relative risk per working level months CI, confidence interval.
Stratification on sub-cohort (2 categories) and age at risk (12 categories).
Maximum likelihood estimates and 95% confidence intervals.

For all bi-cohort analyses, a statistically significant decrease in the risk of lung cancer mortality was found with increasing time since exposure. The ERR/WLM ranged from 0.028−0.040 for radon exposures received 5−14 years previously (results not shown). Only the Czech and Beaverlodge cohort showed evidence of lung cancer risk decreasing with increasing attained age (LR *P* value = 0.02). No exposure rate effect was found among the bi-cohort analysis restricted to < 100 WLM.

6.4.2 Sensitivity analysis using exposure rate ≤ 5.0 WL

A sensitivity analysis restricting the effect modifier analysis on exposure rate (≤ 5.0 WL) rather than < 100 WLM cumulative radon exposure was conducted. In Table 6-12, the radon-lung cancer mortality relationship in the ≤ 5.0 WL was similar to the < 100 WLM restricted analysis. A statistically significant linear increase in the risk of lung cancer mortality with cumulative radon exposure (stratified by sub-cohort and age at risk) was found. This risk decreased significantly with increasing time since exposure. Exposures received 5−14 years previously had more than three times the risk of lung cancer than those received at least 25 years prior. The excess relative risk significantly decreased with attained age. Again, the confidence interval was very wide at 75+ years, for only 27 lung cancer deaths. Finally, a pattern for exposure rate could not be found using this data (LR *P* value ≥ 0.50). These findings indicate that the impact of effect modifiers on the radon-lung cancer mortality relationship was similar at < 100 WLM cumulative radon exposures and ≤ 5.0 WL dose rates.

Table 6-12 Joint cohort restricted to ≤ 5.0WL: excess relative risk and relative risk estimates of lung cancer mortality from the interaction models

Parameter	Deaths	Model A		Model B		Model C		Model D	
		Parameter estimate	95% CI	Parameter estimate	95% CI	Parameter estimate	95% CI	Parameter estimate	95% CI
Total WLM Exposure									
(β) ERR/WLM	616	0.023[a]	0.017−0.032	0.043[a]	0.030−0.061	0.073[a]	0.044−0.120	0.080[a]	0.035−0.166
Effect Modifiers				**Relative Risk**	**95% CI**	**Relative Risk**	**95% CI**	**Relative Risk**	**95% CI**
Time Since Exposure (WLM)									
5−14 years				1.00[b]		1.00[b]		1.00[b]	
15−24 years				0.66[b]	0.42−1.02	0.67[b]	0.43−1.05	0.67[b]	0.42−1.04
25+ years				0.31[b]	0.19−0.47	0.38[b]	0.23−0.60	0.37[b]	0.23−0.60
Attained Age (years)									
< 55	189					1.00[b]		1.00[b]	
55−64	242					0.40[b]	0.19−0.81	0.39[b]	0.18−0.80
65−74	158					0.43[b]	0.19−0.94	0.42[b]	0.18−0.93
75 +	27					0.12[b]	0.00−0.80	0.12[b]	0.00−0.80
Exposure Rate (WL)									
< 0.05	216							1.00[b]	
0.05−0.9	124							0.89[b]	0.50−1.72
1.0−4.9	176							0.92[b]	0.57−1.76
Deviance		3,940.18		3,909.48		3,899.21		3,899.05	
Degrees of freedom		42,471		42,469		42,466		42,464	
Difference in deviance (LR statistic)				30.70		10.28		0.16	
Difference in degrees of freedom				2		3		2	
LR *P* value[c]		< 0.001		< 0.001		0.016		> 0.50	

[a] ERR/WLM for cumulative radon exposure, lagged five years.

[b] Relative risks for time since exposure, attained age, and exposure rate variables; stratification on sub-cohort (3 categories), and age at risk (12 categories). Parameters estimated on the basis of the model below. Here the bracketed area represents the cumulative exposures and parameter estimates obtained in different time windows (5-14, 15-24, and 25+ years previously) and subscript $\boldsymbol{a}$ denotes categories of attained age and the subscript $\boldsymbol{z}$ denotes categories of radon concentration in WL.

$$\boldsymbol{Rate_w} = [\mathbf{1.0} + \boldsymbol{\beta}\,(\boldsymbol{w_{5-14}} + \boldsymbol{\theta_{15-24}}\boldsymbol{w_{15-24}} + \boldsymbol{\theta_{25+}}\boldsymbol{w_{25+}}) * \boldsymbol{\gamma_a}\,\boldsymbol{z_z}]$$

Abbreviations: WL, working levels; WLM, working level months; ERR/WLM, excess relative risk per working level months CI, confidence interval; LR, likelihood ratio; MLE, Maximum likelihood estimate.

Maximum likelihood estimates and 95% confidence intervals.

[c] *P* value from a likelihood ratio test to assess the improvement in fit due to adding additional factors to the model.

6.5 Sensitivity Analysis of the Confounding Effect of Unmeasured Tobacco Smoking

Table 6-13 provides results that reflect the estimates originally presented in Table 6-8, but categories of cumulative WLM were collapsed to correspond to the simplified tables of exposure found in the nested case-control studies that assessed the confounding effect of smoking, as provided by Dr. Nezahat Hunter (refer to Table 5-8). The smoking-unadjusted relative risk was 1.79 for cumulative radon exposures 50–99 WLM compared to the reference cumulative radon exposures < 25 WLM for the joint Czech, French, and Beaverlodge cohort analysis, restricted to < 100 WLM.

Table 6-13 Smoking-unadjusted relative risks by cumulative radon exposure (WLM) for the joint Czech, French and Beaverlodge cohort study, restricted to < 100 WLM

Cumulative radon exposure (lagged five years, WLM)	Mean cumulative radon exposure(WLM)	Lung Cancer Deaths	Person-years	Relative Risk No adjustment for smoking
< 25	10.39	192	325,049	1.00
25–49	36.85	84	35321	1.60
50–99	71.71	132	33,865	**1.79**
Total		**408**	**394,236**	

The reference category (< 25 WLM) has a relative risk set to unity.
Smoking-unadjusted RRs for the primary dataset for analysis (i.e., joint cohort study) were restricted to < 100 WLM and are stratified by sub-cohort (3 categories) age at risk (12 categories) and calendar year period at risk (9 categories).

6.5.1 Method 1: A model for exposure and smoking effects using external prevalence of smoking in categories of radon exposure, and external strength of association

Figure 3 presents the derivation of a bias factor under several assumptions. First, the smoking prevalence in this dissertation's joint cohort correspond to those of Dr. Nezahat Hunter's external special tabulations (2016) of the joint French, Czech, and German miners' nested case-control study. Second, the strength of association of smoking and lung cancer death for current and former smokers, compared to never smokers is RR = 3.85 and

RR = 8.96, respectively (Gandini, Botteri et al. 2008) for both the reference radon exposed miners (< 25 WLM) and radon exposed miners (50–99 WLM). Third, tobacco smoking is not an effect modifier of the radon-lung cancer relationship.

As such, the degree of bias due to smoking was estimated to be 0.916. The resulting smoking-adjusted relative risk is $\mathrm{RR}_{adj} = \frac{1.79}{0.916} = 1.95.$

A multi-dimensional sensitivity analysis was conducted by varying the prevalence of ever smokers in the cohort from about 60% to 80%. Likewise, the smoking-adjusted RR varied depending on the distribution of never, former and current smokers among the reference exposure (< 25 WLM) and exposed (50-99 WLM) scenarios provided from existing case-control data. The range of smoking-adjusted RRs (1.62–2.00) is presented in Table 6-14.

Table 6-14 Range of smoking-adjusted relative risks and bias factors using a smoking-unadjusted relative risk of 1.79 and different smoking prevalence scenarios among unexposed (< 25 WLM) and exposed (50-99 WLM) uranium miners

Reference Exposure (< 25 WLM)			Exposure (50–99 WLM)			Bias factor	Smoking-adjusted RR estimate
never	former	current	never	former	current		
20.4%	**26.7%**	**52.8%**	**30.9%**	**20.2%**	**48.9%**	**0.916**	**1.95**
30.0%	30.0%	40.0%	30.0%	20.0%	50.0%	1.101	1.62
30.0%	40.0%	30.0%	40.0%	20.0%	40.0%	1.050	1.70
40.0%	20.0%	40.0%	30.0%	40.0%	30.0%	0.952	1.87
40.0%	20.0%	40.0%	40.0%	30.0%	30.0%	0.893	2.00
40.0%	30.0%	30.0%	40.0%	35.0%	25.0%	0.940	1.90
35.0%	35.0%	30.0%	40.0%	35.0%	25.0%	0.909	1.96
40.0%	35.0%	25.0%	35.0%	35.0%	30.0%	1.100	1.62
40.0%	50.0%	10.0%	35.0%	50.0%	15.0%	1.000	1.79
30.0%	50.0%	20.0%	35.0%	50.0%	15.0%	0.901	1.98
30.0%	55.0%	15.0%	35.0%	55.0%	10.0%	0.894	2.00
30.0%	15.0%	55.0%	25.0%	15.0%	60.0%	1.069	1.67
20.0%	25.0%	55.0%	25.0%	15.0%	60.0%	1.019	1.75
40.0%	40.0%	20.0%	45.0%	40.0%	15.0%	0.893	2.00
40.0%	40.0%	20.0%	45.0%	35.0%	20.0%	0.962	1.86

RR = 3.85 for former and RR = 8.96 for current smokers, respectively (Gandini, Botteri et al. 2008).
Reference exposure (< 25 WLM) and exposure (50–99 WLM).
Smoking unadjusted RR = 1.79.
$\mathrm{RR}_{adj} = \frac{smoking-unadj\ RR\ (1.79)}{bias\ factor}$

6.5.2 Method 2: A model for exposure and smoking effects using smoking-adjusted estimates from nested case-control studies

Table 6-15 provides the range of smoking-adjusted RRs (2.21–2.72) of lung cancer mortality at 100 WLM, using the smoking-unadjusted RR of 2.7 at 100 WLM from the continuous exposure-response analysis of restricted to < 100 WLM in Table 6-4.

Table 6-15 Smoking-adjusted RR of lung cancer mortality at 100 WLM using the smoking-unadjusted RR of 2.7 at 100 WLM for the joint cohort study and different bias factors from nested case-control studies

Nested case control study	Bias factor	Smoking-adjusted RR estimate at 100 WLM
Hunter et al, 2013 (< 300 WLM) (CZ, FR, GR)	1.22	2.21
Tomášek et al, 2011 (CZ)	1.12	2.41
Leuraud et al, 2011 (CZ, FR, GR)	1.11	2.43
Leuraud et al, 2011 (CZ 1953–, FR & GR 1956–)	1.08	2.50
Leuraud et al, 2007 (FR)	1.07	2.52
Hunter et al, 2013 (< 100 WLM) (CZ, FR, GR)	1.04	2.59
Tomášek et al, 2013 (CZ)	1.04	2.59
Schnelzer et al, 2010 (GR)	1.02	2.66
L'Abbé et al, 1991 (BL)	0.99	2.72

The smoking-unadjusted RR at 100 WLM for the joint cohort study restricted to < 100 WLM was RR = 2.7 at 100 WLM (RR = 1+1.7); the ERR/100 WLM = 1.7
Cumulative radon exposures (WLM) were lagged five years.
Unadjusted-RRs for the primary dataset for analysis (i.e., joint cohort study) were restricted to < 100 WLM and are stratified by sub-cohort (3 categories), age at risk (12 categories) and calendar year period at risk (9 categories).
Nested case-control studies were matched on cohort, attained age and age at birth.
CZ: Czech; FR: French; GR: German; BL: Beaverlodge.
The bias factor due to smoking difference in each nested case-control study equals the $RR_{unadjusted}$ / $RR_{adjusted}$ within the specific nested case-control study.
The joint cohort study's RR adjusted for smoking, equals the joint cohort study's $RR_{unadjusted}$ (2.7) divided by the nested case-control study's bias factor $RR_{adj} = \frac{smoking-unadj\ RR\ (2.7)}{bias\ factor}$

7 Discussion

This study was a joint analysis of Czech, French and Canadian (Beaverlodge) cohorts of male uranium miners, who were first employed as early as 1953, 1956 and 1965 respectively. All three cohorts had long term mortality follow-up periods up to 1999. A total of 394,236 person-years at risk and 408 lung cancer deaths occurred among miners with cumulative radon exposures < 100 WLM. A statistically significant linear relationship between cumulative radon exposure and lung cancer mortality was observed. The ERR/WLM was 0.017 (95% CI: 0.009–0.028), which corresponds to a RR of 2.7 at 100 WLM. Thus, at a cumulative radon exposure of 100 WLMs a uranium miner has 2.7 times the likelihood of dying from lung cancer compared to a miner with zero cumulative exposure. The relationship at < 100 WLM was also highly statistically significant and consistent across the three separate cohorts. For cumulative exposures < 50 WLM, the ERR/WLM was 0.023 (95% CI: 0.008–0.043).

A statistically significant monotonic increase in RR of lung cancer mortality was observed for the joint categorical analysis at < 100 WLM ($P < 0.001$). A statistically significant increase in RR of lung cancer mortality compared to workers with no exposure (0.0 WLM), was first observed at cumulative exposures 10–19 WLM (RR = 1.64; 95% CI: 1.03–2.65). The lung cancer mortality rate increased by almost two and a half times (RR = 2.48; 95% CI: 1.52–4.09) for workers with cumulative exposures 80–100 WLM, compared to workers with no exposure. This was consistent with the continuous ERR/WLM analysis. When analyzed separately, the French and Beaverlodge cohorts had statistically significant increased RRs of lung cancer death ($P = 0.007$, $P = 0.009$) with increased cumulative radon exposure. The

Czech cohort did not have an increased RRs of lung cancer death (P = 0.0157) with increased cumulative radon exposure.

Sensitivity analyses of the impact of potential confounding by unmeasured tobacco smoking by the miners indicated a potential underestimation or overestimation of the association between lung cancer mortality and radon exposure in the multi-dimensional analysis (Method 1). Changes in the prevalence of ever-smokers (60% to 80%) among radon exposed (50–99 WLM) and reference exposed (< 25 WLM) miners may substantially confound the radon-lung cancer mortality relationship. In Table 6-15, the smoking-adjusted RR estimates at 100 WLM from the restricted analyses (CZ 1953–, FR & GR 1956–) of Leuraud and colleagues (2011), and the restricted analyses (< 100 WLM; CZ, FR, GR) of Hunter and colleagues (2013) best reflect the populations of this dissertation's joint analysis. Therefore a smoking-adjusted RR estimate of 2.50– 2.59 at 100 WLM may best reflect the risk estimates of this study.

For effect modifiers, there was a statistically significant decrease in the risk of lung cancer mortality with increasing time since exposure and a non-significant decrease in the risk of lung cancer mortality with increasing attained age. Finally, no exposure rate effect was found at low cumulative exposures (< 100 WLM) or low exposure rates (≤ 5 WL).

7.1 Lung Cancer Mortality Associated with Low Cumulative Radon Exposure

The pattern of results is consistent with that found in an earlier joint analysis of 11 cohorts of miners, in which a significant association between cumulative radon exposure and lung cancer mortality at exposure levels as low as 50 WLM was observed (Lubin, Tomasek et al. 1997). The risk estimates of the Lubin and colleagues study were lower than those of the present analyses: excess relative risks for the < 100 WLM and the < 50 WLM data restrictions were ERR/WLM = 0.008 (95% CI: 0.003–0.014) and ERR/WLM = 0.012 (95% CI: 0.002–0.025) respectively (Lubin, Tomasek et al. 1997).

Considerable work went into improving the quality and quantity of identifying data in the nominal roll and work histories of the Beaverlodge cohort, thus substantially improving the overall quality of mortality linkages (Lane, Frost et al. 2010). All three cohorts had their exposure data updated to more recent time periods (1980s–1999) and mortality follow-up was updated to 1999. This dissertation harmonized the three cohorts to similar mine working conditions (i.e., mechanical ventilation, dose limits, regular high quality radon monitoring) and was restricted on time periods when radon mitigation measures were in place (1956, 1953 and 1965). The extended mortality follow-ups to 1999 for the three cohorts were based on more sources of data (for Beaverlodge) and better quality data than those of the past. Finally, the Czech, French and Beaverlodge cohorts represent 408 lung cancer deaths in this dissertation compared to 159 (77, 33, and 49 respectively) in the < 100 WLM restricted analysis by Lubin and colleagues (1997). As a result of these enhancements, the precision of the risk estimates at low cumulative exposures (< 100 WLM) in this dissertation is substantially greater than those in the earlier joint study of 11 cohorts (Lubin, Tomasek et al. 1997).

The findings in this dissertation are similar to recent analyses (refer to Table 2-1) of extended follow-ups of existing uranium miner cohort studies and nested case-control studies with similar restriction criteria as in this dissertation (Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Tomasek, Rogel et al. 2008, Kreuzer, Fenske et al. 2015, Rage, Caer-Lorho et al. 2015). The French and Czech cohorts used in this dissertation are largely the same cohorts as those used in the above studies, so it is not surprising the results are similar. However, the German study (Kreuzer, Fenske et al. 2015), is a completely separate cohort. It had 334 lung cancer deaths and 846,809 person-years of follow-up to assess the radon-lung cancer relationship at low cumulative exposures with high quality exposure measurements. The joint Czech and French study (Tomasek, Rogel et al. 2008), the French (Rage, Caer-Lorho et al. 2015) and German study (Kreuzer, Fenske et al. 2015), and the French/Czech/German nested case-control study (Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011) and this dissertation were specifically designed to focus on the time periods when mechanical ventilation resulted in dramatic reductions in radon progeny exposures and radon monitoring using high-quality radon measurements became routine (refer to Figure 2). The higher ERR/WLM observed in this dissertation and the above recent studies, compared to the restricted analyses (< 100 WLM, < 50 WLM) of the joint study of 11 miner cohorts (Lubin, Tomasek et al. 1997), reflect the more precise radon measurements compared to extrapolations/estimates made in early mine periods, which resulted in inaccurate risk estimates. They also reflect the extended and improved mortality linkages.

7.1.1 Linear exposure-response relationship

A linear exposure-response model was used in this dissertation. Non-linear models (such as quadratic, linear-quadratic or log-linear) have been assessed in the joint analysis of 11 cohorts of miners, updated studies of radon exposed miners, combined analyses of residential radon case-control studies, and recent cohort studies of residential radon, but have not been found to better fit the data than the linear exposure-response model, even at low exposures (Kreuzer, Fenske et al. 2015, National Research Council 1999, United Nations 2009, Tomasek, Rogel et al. 2008, Hunter, Muirhead et al. 2013, Rage, Caer-Lorho et al. 2014, Darby, Hill et al. 2005, Turner, Krewski et al. 2011, Lubin, Boice et al. 1994, National Research Council 2006). Similarly, the appropriateness of the linear exposure-response relationship was assessed previously in the cohorts used in this dissertation (Tomasek, Rogel et al. 2008, Lane, Frost et al. 2010).

Although non-linear biological mechanistic models (i.e., bystander effect, adaptive response, threshold, and hormesis) are applicable for some *in vivo* and *in vitro* experimental situations, it is not clear that they are relevant to carcinogenesis in humans for low doses and low dose rates of ionizing radiation (Brenner, Doll et al. 2003). Moreover, a white paper on the biological mechanisms of radiation actions at low doses concluded there is a lack of consistency and coherence among mechanistic studies to date (United Nations 2012).

For densely ionizing radiations, as from radon progeny, mechanistic and epidemiological evidence appear to lead to similar conclusions regarding the credibility of the linear model for the estimation of low-exposure risk (Puskin 2003, National Research Council 1999, Samet 2011).

7.2 Impact of Effect Modifiers on the Radon-Lung Cancer Mortality Relationship

A statistically significant decrease in the risk of lung cancer mortality with increasing time since exposure was found. Exposures received more than 25 years in the past had about a third of the risk of lung cancer mortality as exposures received within the last 5–14 years. A statistically non-significant decrease in the risk of lung cancer mortality was found with increasing attained age. However confidence intervals were quite wide at age 75 + years, due to low statistical power in this age category (there were 23 lung cancer deaths in this category). Sparse data affected the fit of models with effect modifiers because of the high degree of stratification within these models. Finally, exposure rate did not have a statistically significant effect on the radon-lung cancer mortality relationship. The confidence intervals were very wide; especially among categories of exposures rates greater than 5.0 WL due to few lung cancer deaths (14). In the sensitivity analysis, which restricted to workers with ≤ 5 WL (616 lung cancer deaths and 419,521 person-years at risk), exposure rate had no statistically significant effect on radon-lung cancer mortality risk.

Time since exposure was the most important effect modifier in this dissertation. The highest ERR/WLM for an effect of radon on lung cancer mortality is observed for exposures received 5–14 years previously. The lung cancer risk associated with cumulative radon exposure received far in the past (≥ 25 years) was significantly lower than the risk associated with radon exposures received 5–14 years ago. Extended mortality follow-up of other cohort studies, and nested-case-control studies of uranium miners also found that, for the same radon exposure, the risk of lung cancer mortality was greatest for radon exposures received in the most recent past (ICRP 2010, Tomasek, Rogel et al. 2008, Hunter, Muirhead et al. 2013, Kreuzer, Fenske et al. 2015, Leuraud, Schnelzer et al. 2011).

In this dissertation, the cohorts were restricted to more recent time periods (1953 onward) to better reflect occupational conditions of current modern miners. Similarly, the above mentioned restricted studies have shorter times of follow-up than unrestricted studies, which include early miners, prior to radiation protection measures in mines (Lubin, Boice et al. 1994, National Research Council 1999, Lane, Frost et al. 2010, Vacquier, Caer et al. 2008, Tomasek 2002, Tomášek 2012, Rage, Caer-Lorho et al. 2015). The higher risk estimates of this dissertation and recent restricted studies may, in part, reflect the shorter times since exposure of miners. Longer follow-up of these restricted cohorts will contribute to improving the estimation of the effect of time since exposure in the future. Time since exposure is perhaps the most important effect modifier of the radon-lung cancer mortality relationship. Alpha particles, from the decay of radon progeny, tend to produce double-strand breaks in cell DNA. Longer exposure intervals would allow more time for repair to occur between multiple hits (Kellerer, Rossi 2012, Thomas 2014). This effect modifier may incorporate the healthy worker survivor effect, competing causes of death over time, improvements in radiation protection over time, and improvements in the quality of exposure measurements and mortality data over time.

Although a statistically significant effect was not found, the risk of lung cancer mortality associated with radon exposure was greatest among the youngest attained ages (< 55 years of age), and decreased with increasing attained age. These findings reflect the results of the joint 11 cohort study at low exposures, (Lubin, Boice et al. 1994, National Research Council 1999, Lubin, Boice et al. 1995) as well as more recent studies of uranium miners restricted to lower exposures or time periods of mechanical ventilation and regular higher quality radon measurements (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013). They also

reflect findings among recent extended cohorts without such restrictions (Villeneuve, Morrison et al. 2007, Lane, Frost et al. 2010, Grosche, Kreuzer et al. 2006, Walsh, Dufey et al. 2010, Kreuzer, Schnelzer et al. 2010, Vacquier, Caer et al. 2008).

An inverse exposure rate effect was observed in many studies of uranium miners, such that the risk of lung cancer for the same total cumulative exposure is greater at low exposure rates than at high exposure rates (Lubin, Boice et al. 1994, Lubin, Boice et al. 1995, National Research Council 1999). However, no exposure rate effect was found at < 100 WLM cumulative radon exposure or ≤ 5 WL exposure rate in this dissertation. At low cumulative radon exposures, an exposure rate effect may diminish or disappear, since at very low doses the probability that more than one alpha particle would traverse a cell is small and there would be no possibility for interactions from multiple hits (Lubin, Boice et al. 1995). The absence of an exposure rate effect was previously reported at < 100 WLM cumulative radon exposures (National Research Council 1999, Lubin, Boice et al. 1994, Lubin, Boice et al. 1995). In the German study of Wismut uranium miners, a strong inverse exposure rate effect was detected for high exposures; however, no significant association was detected at exposures < 100 WLM (Kreuzer, Schnelzer et al. 2010, Grosche, Kreuzer et al. 2006). Akin to this dissertation, a large recent study of long-term exposure at low radon exposure rates among Wismut miners (Kreuzer, Fenske et al. 2015) provided no indication that the ERR/WLM differed by exposure rate at exposure rates < 0.3 WL. The joint French and Czech study could also not demonstrate an exposure rate effect at rates below about 50 WLM/year. Miners in this study were exposed to low exposure rates; no inverse exposure rate effect below 4 WL was observed (Tomasek, Rogel et al. 2008).

Despite the lack of an inverse exposure rate effect at < 100 WLM cumulative radon exposures or ≤ 5 WL exposure rates, it is difficult to determine whether this lack of effect is due to no exposure rate effect at low exposures, or the lack of an ability to detect an exposure rate effect at low exposures because of low statistical power. However, the consistency of findings with other studies suggests that any effect, if it does exist, is likely to be small at low cumulative exposures and exposure rates.

Tobacco smoking was not assessed as an effect modifier in this analysis. However, there is substantial evidence of cohorts with recently extended mortality follow-up that the joint effect of tobacco smoking and radon on lung cancer mortality has somewhere between an additive and multiplicative (sub-multiplicative) interaction (Bruske-Hohlfeld, Rosario et al. 2006, L'Abbé, Howe et al. 1991, Leuraud, Billon et al. 2007, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Tomasek 2013, Tomasek 2011, Amabile, Leuraud et al. 2009, Kreuzer, Brachner et al. 2002).

7.3 Impact of Unmeasured Tobacco Smoking on the Radon-Lung Cancer Mortality Relationship

The last objective of this dissertation was to assess the impact of unmeasured tobacco smoking on the estimates obtained in the joint analysis. Such sensitivity analyses are essential because of the causal importance of tobacco smoking in the etiology of lung cancer (U.S. Department of Health and Human Services. 2014, IARC 2012), the known high prevalence of heavy smokers among miners, and the role of public health campaigns aimed at reducing tobacco smoking. The sensitivity analyses provided a range of possible indirect estimates of the magnitude of confounding due to tobacco smoking had it been possible to control for this directly within the joint cohort study. Two analyses were conducted.

The first method relied on external information about smoking prevalence among miners (controls) and external information on the strength of association (RR) of lung cancer mortality for current, former and never smokers. The prevalence of ever-smokers was then modified from 60%–80% for a multi-dimensional sensitivity analysis. The second method relied on the estimated magnitude of bias from a direct comparison of smoking-adjusted and smoking-unadjusted relative risks of lung cancer at 100 WLM, from nested case-control studies.

Although smoking-adjusted risk estimates by smoking intensity level (number of cigarettes smoked per day) were available from the Colorado Plateau uranium miners and the Newfoundland fluorspar miners; these studies had high cumulative radon exposures, past exposure extrapolations, and the Colorado Plateau study included Navajo miners with very low smoking prevalence (Villeneuve, Morrison et al. 2007, Schubauer-Berigan, Daniels et al. 2009). For these reasons, these studies were considered not appropriate for comparison with

the low cumulative radon exposures and the high prevalence of tobacco smoking among miners in the cohorts of this dissertation.

The indirect smoking-adjusted RRs ranged from 1.62 to 2.00 with the first sensitivity analysis method, compared to the smoking-unadjusted RR of 1.79 for cumulative radon exposures 50–99 WLM compared to the reference < 25 WLM radon exposure, observed in our joint analysis. The results depended on the prevalence of smoking (60% to 80%) and the distribution of never, former and current smokers among radon exposure categories. This method is useful to assess the whole range of the effect the confounder could have on the risk estimate, under varied scenarios of smoking prevalence and strength of association.

A meta-analysis that included studies with incidence and mortality outcomes; studies of different sexes, ethnic groups, and countries; and studies of the general population and occupational groups (Gandini, Botteri et al. 2008) is considered to be the most comprehensive information currently available on the smoking-lung cancer relationship (IARC 2012a). It should be generalizable to uranium miners.

Tobacco smoking also needs to be correlated with radon exposure to be a confounding factor (Breslow, Day 1980). In the first method, the prevalence of tobacco smoking was varied across the reference (< 25 WLM) and radon exposed (50–99 WLM) categories; but the smoking-radon relationship was not necessarily correlated. This resulted in both increases and decreases in the smoking adjusted estimates. Judgement is necessary to ensure the scenarios are realistic, since unrealistic adjustments to the prevalence of tobacco smoking could drastically influence its impact on the risk estimate in this sensitivity analysis.

In the second sensitivity analysis method, using the smoking-unadjusted RR at 100 WLM of 2.7, indirect smoking-adjusted RRs ranged from 2.21 to 2.72 at 100 WLM. All but one older study, which was based of very few lung cancer deaths among Beaverlodge miners (L'Abbé, Howe et al. 1991), found the radon-lung cancer mortality relationship decreased after adjusting for tobacco smoking. This method is a more accurate reflection of what the confounding effect of tobacco smoking had on the radon-lung cancer relationship since it is a direct reflection of findings from recent nested case-control studies of uranium miners with similar smoking prevalence as the cohorts used in this dissertation, and cohorts with low cumulative exposures and quality radon measurements. These results suggest that tobacco smoking does not have a large confounding effect on the radon-lung cancer mortality relationship. The radon-lung cancer mortality relationship persisted and the risk estimates only decreased slightly, after controlling for tobacco smoking in the nested case-control studies (Leuraud, Billon et al. 2007, Amabile, Leuraud et al. 2009, Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013, Tomasek 2011, Tomasek 2013, Schnelzer, Hammer et al. 2010, L'Abbé, Howe et al. 1991). Thus, our smoking-unadjusted risk estimates likely overestimate the true radon-lung cancer mortality effect, but only slightly.

One limitation of the sensitivity analyses was that confidence intervals were not derived. In general, sensitivity analysis with Monte Carlo methods can produce intervals that reflect more than just random error (Shin, Cakmak et al. 2014, Richardson, Laurier et al. 2014). Although Monte Carlo methods would have allowed the estimation of the most likely RR given a reasonable distribution of smoking prevalence and smoking effects, results were instead presented under discrete scenarios that reflect a wide range of smoking patterns that are mostly realistic for modern uranium miners.

The sensitivity analyses also assumed that tobacco smoking was not an effect modifier on the radon-lung cancer mortality relationship. However, the relationship between radon and tobacco is between an additive and multiplicative (sub-multiplicative) interaction (Bruske-Hohlfeld, Rosario et al. 2006, L'Abbé, Howe et al. 1991, Leuraud, Billon et al. 2007, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Tomasek 2013, Tomasek 2011, Amabile, Leuraud et al. 2009, Kreuzer, Brachner et al. 2002).

7.4 Main Strengths

7.4.1 Large sample size

The main strength of this dissertation is that it is a large joint analysis of three cohorts of uranium miners employed after important radiation protection measures were in place. The joint analysis of the Czech, French and Beaverlodge cohorts substantially increased the sample size and statistical power of the individual cohorts (Lane, Frost et al. 2010, Vacquier, Caer et al. 2008, Tomasek 2012) and the joint French and Czech study (Tomasek, Rogel et al. 2008) to assess more precise risk estimates of the radon-lung cancer mortality risk at < 100WLM cumulative radon exposures. The addition of the Beaverlodge cohort to the joint analysis of French and Czech uranium miners resulted in about 30% more lung cancer deaths and person-years of follow-up for cumulative exposures < 100 WLM.

7.4.2 Quality of radon measurements at low cumulative exposures

This dissertation is one of the first large joint cohort studies, with high quality radon progeny exposure measurements, to assess the radon-lung cancer mortality risk among uranium miners who had < 100 WLM cumulative radon exposures. The restricted time frames (1953–1999, 1956–1999, 1965–1999) is especially relevant since radiation protection programs, implemented in the 1950s and 1960s (especially mechanical ventilation, and regular monitoring and measurement of radon gas and radon progeny concentrations), substantially reduced mean occupational radon exposures from > 20 WLM/year to < 5 WLM/year (Tomasek, Rogel et al. 2008, Lane, Frost et al. 2010). These time periods thus reflect times when cumulative radon exposures were low, but not as low as those of today's modern uranium miners (a mean of < 0.3 WLM/year from 2005–2015) (Health Canada 2016) and of good quality.

Measurement error is an important source of bias in occupational cohort studies of uranium miners (Steenland et al. 2003, Rothman, Greenland et al. 2008). However, effort was made to reduce measurement error in this dissertation by restricting the cohort's time periods to when the radon measurements were considered good quality. Measurement error of radon exposures were greatest prior to the late 1950s and 1960s for the Beaverlodge and French cohorts, when ambient radon gas or radon progeny exposure estimates reflected only a few work area measurements per year (Lane, Frost et al. 2010) or expert group assessments (Tirmarche, Raphalen et al. 1993). Routine radon gas monitoring, which began in 1948 in nearly all shafts in Czech mines, produced relatively high quality radon exposure information (Tomasek, Darby et al. 1994). Thus, variation in study-specific measurement error would be far greater in the earlier time periods that were excluded from this dissertation.

An increase in the number and quality of ambient measurements, first of radon gas and then radon progeny concentrations, and the individual monitoring of miners through personal alpha dosimeters (PADs), substantially improved the quality of the radon progeny exposure measurements (Lane, Frost et al. 2010, Tomasek, Rogel et al. 2008).

Stayner and colleagues found that many occupational cohort mortality studies have exposure-response curves with an increasing slope at low exposure levels that attenuates or even turns negative at high exposure levels (Stayner, Steenland et al. 2003). This could occur if there is measurement error in the exposures of exposed workers but not in the exposures of unexposed workers. This is common in occupational epidemiology, in which an unexposed group of workers is used for reference and is clearly unexposed. This phenomenon may also occur when highly exposed workers are subject to more exposure misclassification than those with lower exposures (Stayner, Steenland et al. 2003). Stayner and colleagues found

that the exposure-response pattern becomes increasingly nonlinear and demonstrates a flattening of the exposure-response curve at high exposure levels as the proportion of randomly misclassified persons increases (Stayner, Steenland et al. 2003). Although it is possible that unexposed workers in this dissertation have less misclassification of exposure than workers with the greatest exposures, a large bias is unlikely for two reasons. First, this dissertation is a low radon exposure study (restricted to < 100 WLM) so attenuation would unlikely be observed at these low levels. Second, attempts were made to minimize measurement error by restricting to time periods of quality exposure measurements. The quality of exposures was assessed during the data collection of the updates, and the time periods were restricted to those when quality individual radon measurements were in place. None-the-less, measurement error may still exist within this joint analysis, especially at the earlier times with higher annual exposures. However, Stayner and colleague's attenuation at high exposure levels would be most likely to be observed in the Colorado Plateau miners (Schubauer-Berigan, Daniels et al. 2009) which had extremely high exposures (> 3,000 WLM) which may have been over-estimated because of limited coverage of measurement data (Lubin, Boice et al. 1994).

7.4.3 Quality of mortality outcome data

This joint cohort study had long term mortality follow-up of uranium miners from 1953, 1956, and 1965 to 1999. Almost complete ascertainment of lung cancer mortality information in the Czech and Beaverlodge cohorts was an advantage of this study. The multiple linkages increased both the number and validity of identifying variables and therefore improved the validity of the lung cancer matches of the Beaverlodge cohort to the mortality database (Zablotska, Lane et al. 2013). Although no sub-type information was

available for this dissertation, an earlier analysis of the Beaverlodge cohort (CNSC 2006) assessed the distribution of lung cancer sub-types among lung cancer incident cases (1969–1999). Of 311 lung cancer cases with histology, 35.7% were squamous cell carcinomas, 18.0% were small cell carcinomas, 16.8% were adenocarcinomas, and 30.6% were other types of lung cancer. This information helped to further validate lung cancer deaths (CNSC 2006). The completeness of case ascertainment for Canadian provincial cancer registries is consistently 90–95% (Statistics Canada 2013) (www.naaccr.org/). Similarly, since the registration of deaths is a legal requirement in Canada, reporting of deaths is virtually complete and under-coverage is 1% or less (Goldberg, Carpenter et al. 1993). Thus under-ascertainment of cancer deaths is unlikely.

In the Czech cohort, causes of death have been obtained for 94% of deaths and histology is available in at least 80% of lung cancer deaths in the Czech cohort (Tomasek, Rogel et al. 2008). A limitation that had to be overcome was the French national mortality database. It did not exist before 1968, so about 32% of deaths had missing causes and after 1968 only about 5% (Laurier, Tirmarche et al. 2004). As the French person-year tables were organized by 5 year categories, they were to adjusted for 32% missing causes of death before 1965 and for 28% missing causes of death from 1965–1969. This could potentially underestimate the number of lung cancer deaths in the French cohort and thus underestimate the impact of radon exposure (the French represented 15% of lung cancer deaths in the joint analysis for this dissertation). In fact, the number of missing causes in the cohort before 1968 was very small, so the effect of this correction was also small. But in principle, it needed to be applied [Dr. Ladislav Tomášek, personal communication, March 2017].

Tomasek and colleagues (2008) assessed this in the joint analysis of the French and Czech uranium miners. Fortunately, the impact on the estimated SMRs was very small due to the limited number of deaths with missing causes (42 missing causes out of 136 deaths prior to 1968). Thus, the SMRs for lung cancer mortality in the joint French and Czech cohort were almost identical with and without correction for missing causes, respectively [SMR = 2.87 (95% CI: 2.68–3.08) and 2.82 (95% CI: 2.63–3.03)], so any impact would be small (Tomasek, Rogel et al. 2008). The quality of the French cohort's cause of death information on death certificates and their impact on the exposure-response relationship was studied in detail. The results showed an impact on the estimated global SMR but a very low impact on the exposure-response relationship (Tomasek, Rogel et al. 2008, Laurier, Tirmarche et al. 2004).

7.5 Limitations

In this dissertation, only previously prepared person-year tables, not individual data, were provided. Thus some analytic decisions, such as choice of categorical variable cut-offs, were limited.

7.5.1 Loss to follow-up

In the Czech and French cohorts, cohort membership came directly from company records (Tomasek, Rogel et al. 2008). The French cohort, had a low percentage of miners lost to follow-up (1.0%, n = 33) and there were a low percentage of missing cause of death (2.6%, n = 16) (Vacquier, Rage et al. 2011). In earlier analyses of combined data from the French and Czech cohorts, the proportion of missing causes of death was relatively low (2.4%) (Tomasek, Rogel et al. 2008).

The Beaverlodge cohort was identified from company records or the National Dose Registry (Health Canada 2008). However, 21.8% of the Eldorado cohort, which included Port Radium, Beaverlodge and Port Hope facilities, was lost to follow-up. Port Radium workers (1942-1960) were most likely those lost to follow-up because of limited personal identifiers among early miners (Lane, Frost et al. 2010). This dissertation's restriction of Beaverlodge workers to those first employed from 1965 onward would substantially reduce any influence of loss to follow-up. The social insurance number (SIN) was created in 1964 in Canada. All nuclear energy workers have a regulatory requirement to provide SINs, to permit ongoing dose monitoring through the National Dose Registry (NDR) (Minister of Justice 2000). Most Beaverlodge workers employed since 1965 would have a SIN so the quality of linkages to the NDR, historic tax summary file, and cancer mortality and incidence databases

would be high. Only 7% of workers with a SIN were lost to follow-up in the Eldorado study (CNSC 2004) so the loss to follow-up of Beaverlodge workers in this dissertation is likely < 7%.

7.5.2 Restricted analyses

For time-varying factors, workers contributed to the appropriate category as time progressed. Most miners, regardless of their final cumulative exposures contributed person-years to the restricted exposure dataset (Lubin, Tomasek et al. 1997).Thus all miners, regardless of their final cumulative exposures contributed person-years to the restricted exposure data sets. The deaths, however, would only reflect those of workers with < 100 WLM (or < 50 WLM), since any worker with a greater exposure would have died at a higher exposure level.

A number of alternative analytic methods would have been possible had individual-level records been available. Generally, grouped and ungrouped data provide equivalent results when modelled identically. Ungrouped data (analysis of individual-level records, with each unit of person-time represented separately (Loomis, Richardson et al. 2005) can offer more flexibility in the modelling process, especially as it can avoid categorization of continuous variables. Categorization of continuous variables can result in residual confounding and possibly lead to biased estimates (Richardson, Loomis 2004). Typically, grouped data have been used in analyses of the uranium miner cohorts, with continuous cumulative radon exposures represented as person-year weighted averages. One key assumption necessary for grouped data is that the mortality rate is constant within the defined range of any stratum, something which was not testable in this dissertation.

Another possible limitation of the main analysis for the first study objective, relates to restriction of cumulative exposure to a maximum of 100 WLM. Person-year strata at cumulative exposures greater than 100 WLM were removed in the "restricted analysis". This removal of strata may have introduced a bias. In effect, the restriction censored follow-up for individuals who may have accumulated more exposure and eventually developed and died from lung cancer at a later time, despite the earlier and lower exposure causally affecting the risk of lung cancer death. A recent study of German uranium miners also restricted radon exposures to < 100 WLM and < 50 WLM (refer to Table 2-1). This resulted in a significant ERR/WLM of 0.016 or 0.013, respectively (Kreuzer, Fenske et al. 2015) Alternatively, modelling the unrestricted follow-up and instead only reporting excess relative risk estimates in the range of 0–100 WLM would have potentially allowed bias from measurement error at higher levels of exposure, which were predominantly accumulated in the earlier time periods. For this reason, the ERR were estimated and presented from both restricted and unrestricted analyses. Had individual-level data been available, an alternative strategy would have been to analyze only those individuals with lifetime exposure of less than 100 WLM.

7.5.3 Healthy worker survivor bias

Healthy worker survivor bias is a continuing selection process whereby workers with poorer health accrue less exposure (i.e., reduce their work hours, do less strenuous work, leave work, or retire prematurely) compared with their healthier counterparts. This bias results when comparing workers with long versus short term work durations. It is especially true for strenuous jobs, such as underground mining (Bjor, Damber et al. 2015, Buckley, Keil et al. 2015). If occupational data are not analyzed appropriately, the exposure of interest (radon progeny) may appear to be protective or less harmful (Buckley, Keil et al. 2015, Checkoway,

Pearce et al. 2004, Steenland, Deddens et al. 1996). The healthy worker survivor bias to be greater for diseases with chronic morbidity (i.e., cardiovascular diseases) compared to cancer. For cancer, the effect is smaller for incidence than for mortality since those with a cancer diagnosis are likely to alter their employment status. The survival rate of the cancer may also impact the effect (Breslow, Day 1987). Time related factors (age at hire, age at risk, duration of employment), socioeconomic status, and gender may also influence this bias (Shah 2009, Buckley, Keil et al. 2015). The potential for a healthy worker survivor bias was addressed in this dissertation through several approaches.

7.5.3.1 Lag time and duration of employment restrictions

First, cumulative radon exposures were lagged by five years to address any changes in cumulative radon exposures as a result of a worker's lung cancer. Second, workers were restricted by duration of employment so short-term workers were excluded. Short-term workers are known have higher mortality rates than long-term workers, unrelated to occupational radon exposures (Bjor, Damber et al. 2015, Buckley, Keil et al. 2015). The severely ill or chronically disabled (i.e., asthmatics, physical impairments) are often less able to remain employed, especially in strenuous jobs like underground mining. Similarly, there are many health benefits of work, such as improved access to healthcare, routine medicals, health insurance, physical activity and socialization (Arrighi, Hertz-Picciotto 1994, Picciotto, Hertz-Picciotto 2015).

Results (refer to Table 5-4) suggested that short term workers did not have higher crude mortality rates. However, a sensitivity analysis found the ERR/WLM for Beaverlodge workers with less than six months employment was almost twice the risk of workers employed at least six months, although this was not statistically significant. The

ERR/WLM = 0.017 (95% CI: no convergence–0.063; *P* = 0.265; N = 74; range = 0–99.5 WLM; mean = 9.97 WLM) for short term workers. For workers employed at least six months, the ERR/WLM = 0.0091 (95% CI: 0.005–0.015; N = 195). However, when these workers were restricted to < 100 WLM, the ERR/WLM = 0.021 (95% CI: 0.008–0.044; *P* < 0.001; N = 123; range = 0–99.9 WLM; mean = 32.3 WLM) respectively. These worker's range of cumulative exposures were similar to those of short term workers; however, their mean exposure was three times higher, and their ERR/WLM was within the same confidence interval range of short term workers. This suggests that short term workers were not significantly different from workers with < 100 WLM. However, for consistency with the Czech and French, and because of their unique characteristics (high proportion workers with age at risk age 16–29 years and cumulative exposures < 5 WLM), we excluded short term workers.

7.5.3.2 Immortal time

To address a possible healthy worker survivor effect caused by short-term workers, the start of follow-up began after four years of employment in the Czech Jáchymov cohort and after one year of employment in the Czech Příbram and French cohort, to exclude the "immortal" person-time created by these cohort entry restrictions. Immortal person-time bias arises when follow-up time is included as "at risk" for the study outcome despite "survival" to cohort entry being a criterion (i.e., minimum of four or one years of employment) (Suissa 2008). Unfortunately, the exclusion of miners employed for less than six months, so as to address a possible healthy worker survivor effect, introduced immortal time bias in the Beaverlodge cohort. This was because it was not possible to exclude the first six months "at risk" person-time from tabulations of Beaverlodge workers employed for more than 6 months. Their start

of follow-up began the first day of employment rather than after the first six months had passed. This overestimated the person-years of long term Beaverlodge workers by six months and therefore could underestimate the radon-lung-cancer relationship. The range of duration of employment was 0–46 years among Beaverlodge miners (mean = 3 years) [Dr. Lydia Zablotska, personal communication, 2016-12-11].

The potential healthy worker survivor bias of short term workers was assessed to have a more important impact than the bias introduced by a 6 month immortal time bias. There were many (74 lung cancer deaths, 97,617 person-years) short term workers among Beaverlodge miners, with very different characteristics compared to long term Beaverlodge miners. Short term workers would skew the distribution of employment time at very low cumulative radon exposures (Table 5-3 and Table 5-4). Thus, the Beaverlodge cohort would be considerably different than the Czech and French cohorts, had short term workers not been excluded.

7.5.3.3 Prevalent and incident hires

Only “incident hires”, which started work on or after 1953 or 1956 in the Czech and French cohorts, respectively were included. These calendar year restrictions were done using each cohort’s individual data. Workers employed prior to these dates were excluded.

However, since only person-year tables were available for the Beaverlodge cohort, “prevalent hires” were introduced into the cohort by excluding calendar years at risk before 1965. Workers who were first hired before 1965 were still retained, but their person-time contributions before 1965 were excluded. About 13% (37,265 person-years) of total person-time occurred from 1950–1964.

The impact of prevalent and incident hires, based on the worker's date of hire before or after the start of follow-up, on the healthy worker survivor bias was assessed in two recent occupational cohort studies (Applebaum, Malloy et al. 2007, Costello, Friesen et al. 2011). Despite the loss of statistical power and a restricted exposure range, decreasing the relative proportion of prevalent to incident hires reduced healthy worker survivor bias, resulting in stronger evidence for a dose-response between occupational exposures and cancer mortality (Applebaum, Malloy et al. 2007, Costello, Friesen et al. 2011).

Two sensitivity analyses (refer to section 6.2.1, Table 6-6) were conducted to assess the impact of prevalent hires on the Beaverlodge cohort. The risk estimates in this dissertation may be slightly overestimated, but there was not a big influence of these prevalent hires on the exposure-response relationship.

7.5.3.4 Open pit and mill workers, workers with 0.0 WLM cumulative exposures, and age censoring

The joint analysis includes French open pit miners and Beaverlodge mill workers. All these workers have some radon exposures. Analysis of these workers provided no evidence that these workers were less healthy than underground miners (Lane, Frost et al. 2010, Vacquier, Rogel et al. 2009).

Workers with cumulative exposures of 0.0 WLM were included in this joint cohort as the reference population since all job types included some workers with 0.0 WLM cumulative exposures. There was no evidence that they were systematically different from those with higher exposures. The measures taken in this dissertation should help reduce the impact of any healthy worker survivor bias in this joint cohort study.

The Czech and French cohorts were censored at age 85 years to reduce potential bias due to missing information and uncertainty of diagnoses in older age categories (Rage, Vacquier et al. 2012, Tomasek, Rogel et al. 2008). Follow-up in the Beaverlodge cohort was censored at age greater than 100 year if no death was found (Lane, Frost et al. 2010). The highest age stratum, 85–100 years would reflect deaths and person-years at risk from follow-up among Beaverlodge miners. There were no deaths and 485.3 person-years at risk among Beaverlodge workers age 85–100 years with < 100 WLM cumulative exposures, which suggests that censoring at age 85 had minimal impact on this analysis (refer to Table 5–6).

7.5.3.5 G-methods

Robins (1986) developed a family of methods known as G (generalized) methods that focus on potential outcomes, or outcomes that would be observed for an individual worker under a particular exposure history. These methods of analysis are potentially valuable when employment status is a time varying confounder affected by prior exposure. G-methods have recently been applied to account for employment status of radon-exposed miners (Keil, Richardson et al. 2015, Bjor, Damber et al. 2015, Edwards, McGrath et al. 2014) and suggest that these new methods result in less biased risk estimates than standard methods (lagging, restriction, stratification). Although software is available, these methods require considerable analytical effort (Buckley, Keil et al. 2015) so were not undertaken for this dissertation with group person-year data.

7.5.4 Lung cancer mortality versus lung cancer incidence

Lung cancer mortality, not incidence, was assessed in this dissertation because information on cancer incidence was not available for the Czech or French cohorts. Cancer incidence is the preferred outcome measure for analysis because several factors can influence the likelihood of cancer survival, unrelated to occupational radon exposure. These include the cancer stage at diagnosis, aggressiveness of the tumour, the availability and quality of early detection, diagnostic and treatment services. Factors such as age, sex, existence of other health conditions, socio-economic status and lifestyle can affect survival (Canadian Cancer Society 2016, Canadian Cancer Society 2013). Therefore, use of lung cancer mortality as the outcome can potentially underestimate the true radon-lung cancer risk. However, the five-year survival, a measure of disease severity and prognosis, is very low for lung cancer (overall 14% for men in Canada); so most men diagnosed with lung cancer die from it within 5 years. Lung cancer mortality will thus largely reflect lung cancer incidence (Canadian Cancer Society 2016, Canadian Cancer Society 2013).

Doria-Rose and Marcus (2009) found that death certificates were sufficiently accurate when assigning lung cancer as the underlying cause of death in the Mayo Clinic Lung Project in Minnesota, United States (Doria-Rose, Marcus 2009). Studies of the Eldorado uranium workers, which included Beaverlodge workers, found very similar results when assessing lung cancer incidence and mortality (Lane, Frost et al. 2010, Zablotska, Lane et al. 2013). In the Czech cohort, the original records of causes of death were compared with data for compensated miners. Very few lung cancer deaths were not reported at local registries or reported in the compensation files (Tomasek, Rogel et al. 2008).

7.5.5 Sensitivity analysis of unmeasured tobacco smoking

Two sensitivity analyses were used to quantify the likely range of confounding, providing a necessary input to the interpretation of the smoking-unadjusted results.

The two methods resulted in slightly different derived smoking-related bias factors. The first method varied several parameters that govern the bias to understand how sensitive the results are under different plausible assumptions of smoking prevalence (based on prevalence of tobacco smoking by cumulative radon exposure categories) and the strength of the smoking-lung cancer mortality association. The smoking-related risk estimates among former and current smokers (Gandini, Botteri et al. 2008) were assumed to be generalizable to uranium miners for the purposes of the analysis. Although the meta-analysis by Gandini and colleagues included a few occupational studies, they were not specific to uranium miners and most studies were taken from the general population. Similarly, the definition of "former" and "current" smoker can vary across studies, and not reflect the definitions of "ex-smoker ≥ 10 years" and "ex-smoker < 10 years or current smoker" used for the prevalence of tobacco smoking among exposed (50–99 WLM) and reference level (< 25 WLM) exposed miners used in this dissertation (Hunter, Muirhead et al. 2013). Finally, tobacco smoking information was limited to smoking status.

Smoking intensity (cigarettes smoked per day, duration of smoking) may be a better measure to use; higher ERR/WLMs were observed among those who smoked a greater number of cigarettes daily in the recently updated Newfoundland fluorspar miners study. Unfortunately, this information was not available at exposures < 200WLM (Villeneuve, Morrison et al. 2007). Likewise, the SMR increased with the number of packs smoked per day among the

Colorado Plateau miners, but no information was available at cumulative radon exposures < 120 WLM (Schubauer-Berigan, Daniels et al. 2009).

We further imposed a simplifying assumption on our model, that the effect of radon was constant across levels of smoking. This assumption is likely incorrect, since the joint effect of tobacco smoking and radon has been observed to be somewhere between an additive and sub-multiplicative interaction. However, data have only been available in a few mining cohorts, and with rather simplistic data on smoking (Leuraud, Schnelzer et al. 2011, Tomasek 2013, Hunter, Muirhead et al. 2013, Lubin, Boice et al. 1994, National Research Council 1999, Leuraud, Billon et al. 2007).

The second method is likely to better reflect the bias due to smoking that actually existed in the joint cohort analysis for this dissertation. This is because it derives from nested case-control studies of cohorts of uranium miners that are fairly representative of the uranium mining populations used in this dissertation. In Method 2, the joint nested case-control study of French, Czech and German uranium miners restricted to < 100 WLM (Hunter, Muirhead et al. 2013) and restricted to the later time periods (Czech 1953–1999 , French & German 1956–1994) (Leuraud, Schnelzer et al. 2011) was thought to be the most reflective of the joint cohort study in this dissertation. These two restricted analyses included two out of the three cohorts used in the primary dataset being analyzed (the Czech and French cohorts). The larger size of the joint nested case-control study provided more accurate estimates of RRs of lung cancer mortality at low cumulative radon exposure, or at time periods when high quality radon progeny measurements were used, adjusting for smoking, compared to the country-specific nested case-control studies (Tomasek 2011, Schnelzer, Hammer et al. 2010, Leuraud, Billon et al. 2007, L'Abbé, Howe et al. 1991) or the whole unrestricted nested-

case-control study (Leuraud, Schnelzer et al. 2011). None-the-less, measures of smoking exposure were very crude (never smoker, ex-smoker who had stopped smoking 10 years or more previously, and either current smoker or ex-smoker who had stopped smoking within the last 10 years) in this sensitivity analysis. This would have implications for residual confounding, even if direct adjustment had been possible.

Blair and colleagues argue that examples of substantial confounding are rare in occupational epidemiology (Blair, Stewart et al. 2007). In studies of occupational exposures and lung cancer, tobacco-adjusted relative risks rarely differ appreciably from the unadjusted estimates (Blair, Stewart et al. 2007). Likewise, many findings on other well-established human carcinogens indicate that confounding, in occupational studies of lung cancer is rare and is not likely to be an explanation for positive study findings (L'Abbé, Howe et al. 1991, Bruske-Hohlfeld, Mohner et al. 2000, Axelson 1978, Lubin, Pottern et al. 2000, Levin, Zheng et al. 1988, Richiardi, Forastiere et al. 2005, Siemiatycki, Wacholder et al. 1988, Welch, Higgins et al. 1982). The results of the sensitivity analyses in this dissertation tend to support the argument by Blair and colleagues (2007).

7.5.6 Other confounding factors

Other known human carcinogens might have resulted in confounding of the estimates in this dissertation. These include gamma radiation, long-lived alpha radionuclides, residential radon, arsenic, silica, and diesel exhaust (IARC 2013, IARC 2012a, IARC 2012b). If any confounding effect were to occur, individually this would be expected to be less than that of tobacco smoking because of their lower strength of association with lung cancer and lower levels of exposures (as far as this limits the correlation with WLM) in comparison to tobacco smoking. Blair and colleagues argue that if tobacco use does not confound lung cancer risks in occupational studies, it is even less likely those more modest risk factors for various diseases and with no known association with the exposure of interest would have a substantial effect (Blair, Stewart et al. 2007).

Gamma radiation was not a significant confounding factor in the Beaverlodge (Lane, Frost et al. 2010) or German (Walsh, Tschense et al. 2010) uranium miner cohorts. Although there was a statistically significant confounding effect of gamma radiation in the French post 1955 sub-cohort, cumulative exposures and absorbed lung doses of external γ-ray dose and radon were highly correlated (Rage, Vacquier et al. 2012). Minimal confounding effect was found for long-lived radionuclides (LLR) in the German cohort (Kreuzer, Dufey et al. 2015, Walsh, Tschense et al. 2010). In French miners, although LLR had a borderline significant relationship with lung cancer mortality, it had very large confidence intervals, was highly correlated with radon progeny exposure, and represented only 1.3% of the alpha particle absorbed lung dose (Vacquier, Rage et al. 2011, Rage, Caer-Lorho et al. 2014, Rage, Vacquier et al. 2012). Information on the relationship between gamma and LLR on lung

cancer mortality was not available for the Czech cohort (Sabol, Jurda et al. 2011, Marusiakova, Gregor et al. 2011, Otahal, Burian et al. 2014).

Overall, the Beaverlodge and Czech mines had low mineral ore content of crystalline silica (Leuraud, Schnelzer et al. 2011, Lane, Frost et al. 2010) so it was not relevant. In French miners, the radon-lung cancer mortality relationship persisted after adjustment for silicotic status (Amabile, Leuraud et al. 2009). The Beaverlodge and French mines had low arsenic content in the ore (Leuraud, Schnelzer et al. 2011, Lane, Frost et al. 2010) so it was not relevant. The Czech Jáchymov miners, first hired from 1953–1959, may have some confounding effects of arsenic (those from 1948–1952 were excluded). Unfortunately, precise estimates of miners' arsenic exposure are not available. The mean percentage of arsenic in the dust was 0.5% (maximum 7.1%) in Jáchymov (Tomasek, Darby et al. 1994). Diesel equipment was not used in Czech mines because it was electrically powered [Dr. Ladislav Tomášek, personal communication, 2016-07-07] and diesel was only introduced in the 1970s–1980s in the French and Beaverlodge mines, respectively.

Diesel exhaust is more likely to be an important confounder in modern uranium mines than in the time-frames of the cohorts used in this dissertation. Finally, there was no information available on the relationship between uranium miners' domestic radon exposures in relation to occupational radon exposures. This should be an area of future research especially since cumulative domestic radon exposures may exceed modern miners' cumulative occupational radon exposures over a lifetime. Residential radon is related to socio-economic status; people with higher SES who live in single family homes have higher residential radon exposures compared to people of lower SES who live in multiple family dwellings (AGIR 2009).

7.5.7 Limited assessment of effect modifiers

Another limitation of having prepared person-year tables was the limited assessment of potential effect modifiers. This study was limited to the assessment of radon exposure in time since exposure windows, attained age and exposure rate (the BEIR VI exposure-age-concentration model).

Other studies have assessed effect modification by age at exposure (first, median), time since exposure (first or median) exposure, quality of exposure estimates (estimated/measured), period of exposure, duration of exposure, physical activity level, job type, and mine type. These studies have advanced the understanding of effect modifiers on the radon-lung cancer mortality relationship at low cumulative exposures (Kreuzer, Fenske et al. 2015, Tomasek 2012, Tomasek 2014, Tirmarche, Harrison et al. 2012, Tomasek, Rogel et al. 2008). However, the ERR/WLM was not modified by duration of exposure in recent German uranium miners (Kreuzer, Schnelzer et al. 2010, Grosche, Kreuzer et al. 2006).

This dissertation was restricted to only time periods when measurement of radon progeny became routine so it was not possible to assess the potential effect modification by the quality of exposure estimates or period of exposure. Other recent studies found the risk of lung cancer was greater among ‘measured’ exposures or more recent time periods (Tomasek, Rogel et al. 2008, Vacquier, Caer et al. 2008, Kreuzer, Fenske et al. 2015, Hunter, Muirhead et al. 2015, Leuraud, Schnelzer et al. 2011).

Further analysis of effect modifying factors may improve our understanding of their impact on the radon-lung cancer mortality relationship. None-the-less, the consistency of the findings in this dissertation using time since exposure, attained age, and exposure rate with

other recently published studies suggests that these are still appropriate when assessing the risk of lung cancer mortality in miners with relatively high quality and low cumulative radon exposures.

7.5.8 Heterogeneity

Heterogeneity among the French, Czech, and Beaverlodge cohorts was first reduced by restricting the time period to eras when radon mitigation measures were in place, and quality radon progeny exposures were required for regulatory purposes. However, the Beaverlodge cohort (1965–1999) had the highest cumulative radon exposures (mean: 118.5, max.: 1,617 WLM) and exposure rates (mean: 2.64, max.: 29.4 WL); the French cohort (1956–1999) had the lowest (mean: 36.4, max.: 127.7 WLM; mean: 0.27, max.: 7.04 WL). The cohorts were then restricted to < 100 WLM cumulative radon exposures, and excess risk estimates were stratified by sub-cohort, age at risk and calendar year at risk. Finally, the risk effect modifier analysis considered the modifying effects of radon exposures by time since exposure, attained age and exposure rate.

Large differences between the French and German miners were also observed in the European nested-case-control study (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013). In fact, the German sample had even higher mean cumulative exposures (688 WLM for cases, 440 WLM for controls) than Beaverlodge, compared to the French (101 WLM for cases, 59 WLM for controls). Restricting the nested case-control study to cumulative exposures < 300 WLM made the country specific studies homogeneous (Hunter, Muirhead et al. 2013). Similarly, the ERRs/WLM per country in the late period (which is consistent with the joint cohort study in this dissertation: 1953, 1956) were not significantly different (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013).

7.6 Implications

This dissertation, a large joint analysis of three cohorts of uranium miners, provided new and more precise risk estimates of the effect of low cumulative radon exposures (< 100 WLM) on the risk of lung cancer mortality. These risk estimates represent radon-lung cancer risk of miners who first worked during time periods when significant improvements in radiation protection resulted in dramatic reductions in occupational radon exposures and exposure rates and quality radon measurements became routine. This dissertation found higher and more precise risk estimates than in previous analyses at low exposures (Lubin, Boice et al. 1995, Lubin, Tomasek et al. 1997). Earlier studies included earlier time periods of uranium mining without radiation protection, and estimated or extrapolated radon estimates. However, the lung cancer risk of cumulative radon exposure is still low.

This dissertation also found that unmeasured confounding by tobacco smoking has contributed to slightly over-estimated risk from radon exposure, using the most realistic scenarios of smoking patterns, as indicated in Model 2 of the sensitivity analysis.

Recent annual radon progeny exposures (refer to Table 3–1) were estimated by the National Dose Registry (Health Canada 2016). The mean annual radon progeny exposures of Canadian uranium miners from 2005–2015 ranged from 0.016–0.209 WLM and the sum of ten-years average annual radon exposures was 1.8 WLM. In a 30 year career of a uranium miner, an average cumulative radon exposure would be expected to be about 5.5 WLM. Since the trend in occupational radon exposures suggests continued reduction in exposure and the average duration of employment is less than 10 years (Lane, Frost et al. 2010, Vacquier, Rogel et al. 2009, Tomasek, Rogel et al. 2008), most miners would receive much less than 5.5 WLM.

Occupational dose limits around the world are largely based on the recommendations of the International Commission on Radiological Protection (ICRP 2007). Currently, the occupational dose limit is 100 mSv over 5 years, without exceeding 50 mSv per year. These are the dose limits in other countries with uranium mining, such as Kazakhstan, and Namibia. In Niger the dose limit is 20 mSv per year. Although the same standards are applied worldwide for radiation protection, not all countries necessarily achieve the same dose levels. Radiation protection is based on ALARA (as low as reasonably achievable, social and economic factors considered). Thus, in open pit mining in Namibia and Niger, dose limits are very similar to open pit mining in Canada. However, low grade underground mining, is a challenge. Thus, for example, in Niger the average radon progeny exposure in 2013 was about 2.66 mSv/year (0.532 WLM/year) and the maximum was 7.48 mSv/year (1.496 WLM/year) [Mr. Dale Huffman, VP, HSE & RR; AREVA Resources Canada, personal communication, March 2017]. In this dissertation, a statistically significant increase in the risk of lung cancer mortality was first found at cumulative exposures of 10–19 WLM (RR = 1.64; 95% CI: 1.03–2.65). Thus, miners in other countries could reach cumulative radon exposures that significantly increase their risk of lung cancer if radiation protection is not strictly regulated.

A linear non-threshold dose response relationship between ionizing radiation and cancer has been observed in diverse populations, with different radiation sources, and different experimental designs (United Nations 2012, United Nations 2008, National Research Council 1999, National Research Council 2006). However, given the very low cumulative exposures modern miners now receive, and the increased risk estimates in studies restricted to low radon exposures using more accurate exposure measurements (refer to Table 2-1)

(Tomasek, Rogel et al. 2008, Kreuzer, Fenske et al. 2015, Rage, Vacquier et al. 2012, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011), it is critical that this assumption be challenged.

Modern Canadian uranium miners' cumulative occupational radon exposures are well below the levels where a statistically significant increased risk of lung cancer mortality was observed in this dissertation. However, a very high level of radiation protection is critical to ensure current uranium miners' exposures continue to be ALARA. This is especially important in modern uranium mines, such as the McArthur River and Cigar Lake mines in Northern Saskatchewan, which are the world's first and second largest high-grade uranium mines (CNSC 2014). Any lapse in radiation protection could quickly expose workers to very high radiation exposures. However, uranium miners using more traditional mining methods, especially in other countries, have higher average annual radon progeny exposures than miners in high grade ore mines. These miners have the greatest risk of receiving cumulative radon exposures at the levels when the risk of lung cancer is statistically significant.

7.7 Future Research

Epidemiological studies of uranium miners are important and should focus on the long term follow-up of miners after radiation protection measures resulted in high-quality radon measurements, low cumulative radon exposures and low exposure rates. These studies best reflect the radon-lung cancer mortality relationship of current uranium miners whose radon exposures may be too low to feasibly initiate a modern cohort study (CNSC 2003). Large sample sizes, though the combining of several cohort studies and long-term mortality follow-up of existing cohorts are necessary to provide the statistical power to assess different aspects of this risk relationship precisely. Further modelling work is warranted at low exposure levels, to readdress whether the effects there are linear, but this will be limited to the large combined cohorts. Different potential effect modifiers should be incorporated into the analysis of the radon-lung cancer mortality relationship at low cumulative exposures to further understand the factors that affect the relationship.

Cancer incidence and mortality should be assessed together in the cohorts where cancer incidence is available, and histological information would help to identify specific cell types (i.e., squamous cell, small cell) of radon-induced lung cancer. Other causes of death should continue to be monitored to ensure that workers are not at risk of other health outcomes (i.e., leukaemia from external gamma radiation in mines (Kreuzer, Sobotzki et al. 2016, Zablotska, Lane et al. 2014)).

Current uranium miners should be added to existing cohort studies. For example, modern Saskatchewan uranium miners (1970s onward) should be incorporated into the Beaverlodge cohort. Similarly, other radiation exposures and other human carcinogens in the mine environment should be included in exposure-monitoring programs to track trends in

exposures now and in the future. For example, diesel emissions in Saskatchewan uranium mines today [Mr. Stan Frost, personal communication, 2015-02-11] should be monitored and incorporated in existing studies to assess their confounding effects. Data from such programs could be useful for better estimation of future exposure reductions and for evaluating concomitant reductions in human lung cancer risk while avoiding the need for historical reconstructions of exposure (HEI Diesel Epidemiology Panel 2015).

Tobacco smoking is the primary cause of lung cancer and uranium miners are known to be heavy smokers (U.S. Department of Health and Human Services. 2014, IARC 2012). The quality of tobacco smoking information collected on uranium miners should be improved (completeness of smoking information, precision of smoking exposure: cigarettes smoked per day, duration of smoking) and incorporated into cohorts or nested case-control studies. This would improve the understanding of the confounding effect and the interaction between tobacco smoking and radon exposure, especially as the prevalence of tobacco smoking changes.

Residential radon is the second leading cause of lung cancer and residential radon exposures over a lifetime are likely to far exceed occupational radon exposures (IARC 2012, United Nations 2009). Information on uranium miner's residential radon exposures should be collected and incorporated into cohorts or nested case-control studies to determine the impact this potential important confounding factor has on the occupational radon-lung cancer mortality relationship and to assess the lung cancer risk of cumulative residential and occupational radon exposures in uranium miners.

Existing cohorts should continue to extend their mortality and cancer incidence follow-up. The Czech, French, German and Ontario uranium miners studies have been recently updated to 2010, 2007, 2013, and 2007, respectively (Kreuzer, Sobotzki et al. 2016, Tomasek 2012, Rage, Caer-Lorho et al. 2015, Navaranjan, Berriault et al. 2016). The Beaverlodge cohort is planned to be updated in the near future. Both Canadian cohorts have cancer incidence follow-up. Extending the mortality follow-up of existing cohort studies is especially important if cohorts are restricted to time periods of quality radon exposures because this has reduced the cohort's length of follow-up and includes more recent miners. Only about 30%, 25%, and 40% of Beaverlodge, French and Czech uranium miners had died by 1999, 1994 and 1995, respectively (Lane, Frost et al. 2010, Vacquier, Caer et al. 2008, Tomasek, Rogel et al. 2008). Thus, it is still very important to update these cohorts. Uranium miners employed since the 1950s and 1960s are now reaching ages when cancer and chronic disease mortality rates are high. Therefore extending follow-up will result in the substantial increase in lung cancer deaths and person-years of follow-up. Finally, joint analyses of more cohorts with high quality exposure measurement restricted to low cumulative radon exposure are necessary. Extending the current joint cohort analysis to include the recently updated German and Ontario cohorts would significantly increase the number of lung cancer deaths and person-years of follow-up, and add more information on confounding factors and effect modifiers.

8 Conclusion

The present joint analysis of male uranium miners confirms a statistically significant linear increase in the risk of lung cancer mortality at < 100 WLM cumulative radon exposures. This was based on 408 lung cancer deaths and 394,236 person-years of risk from the Czech, French and Canadian male uranium miners, employed in 1953 or later.

Consistent with other studies focused on high quality, low cumulative radon exposures, time since exposure was an important effect modifier. Cumulative radon exposures received in the more recent past (5–14 years prior) had a greater risk of causing lung cancer mortality compared to exposures received in the more distant past (25 + years prior). Risk of lung cancer was greatest among those < 55 years of age and risk decreased with increasing attained age. However, this relationship was not statistically significant. Finally, no effect of exposure rate was found in this analysis, consistent with other studies at low cumulative exposures and low exposure rates.

A sensitivity analysis of the potential confounding effects of tobacco smoking on the radon-lung cancer relationship was conducted using external information. The narrow range of smoking-adjusted risk estimates suggests that adjusting for tobacco smoking would not have materially changed the interpretation of previous estimates of the radon-lung cancer effect. However, changes in the distribution of the prevalence of tobacco smoking among the heavy smoking uranium miner population could substantially overestimate or underestimate risk, as indicated in our first sensitivity analysis. It is critical to collect quality smoking prevalence information to control for this confounding factor.

The results in this dissertation are broadly consistent with other studies of uranium miners with high quality radon exposure measurements at low cumulative radon exposures or exposure rates and with studies of residential radon. Precise quantification of the risk of lung cancer at low levels of radon exposure and the factors that confound and modify this risk are essential for ongoing occupational radiation protection.

Appendix A: Population, Exposure and Outcome Characteristics of the Beaverlodge, French and Czech Uranium Miners

Cohorts of Uranium Miners			
	Beaverlodge Cohort	**Czech Cohort**	**French Cohort**
Description of miners	This dissertation includes the Beaverlodge cohort of male uranium mine and mill workers, as described in a previous publication (Lane, Frost et al. 2010). Employee information came from the personnel files provided by the mines and processing sites of Eldorado Nuclear Ltd. The date of entry into the cohort corresponds to first day of employment. The personal identifiers included as much information as available (surname, first, second, etc. names, maiden name, date and place of birth, sex, marital status, SIN, UIC, last year known alive, data on spouse, parents and children). The Beaverlodge mine (in northern Saskatchewan, Canada) operated from 1948 to the final shutdown of mine in June 1982. Designation of a worker to Beaverlodge reflected the site at which he spent his longest period of employment for Eldorado; similarly, underground and mill workers were defined by the job held for the longest time.	The study population of the cohort consists of male underground miners exposed in two different periods. Uranium miners from the Jáchymov region in west Bohemia (who began underground work from 1948–1959) and uranium miners who entered the Příbram mines in central Bohemia from 1968–1974.	Uranium mining began in France starting in 1946 with the CEA. Mines were located in the four main areas in France (Vendée, Limousin, Forez and Hérault), with different periods of operation. Since 1976, COGEMA has operated the mines. Mining and milling at these sites ended in 2001.
Study population/ Inclusion criteria	For inclusion onto the Eldorado nominal roll, employees had to be on the payroll for one day or more, employed during the ages 15–75 years for Eldorado from 1932–1980, had their last contact after 1940, and were known to be alive at start of follow-up in 1950 (mortality analysis). The cohort used in this dissertation includes Beaverlodge workers first exposed from 1965 onward .Refer to the section of thesis titled: Harmonizing the cohorts of uranium miners by time periods of radiation protection measures and quality of radon exposure assessment**.**	The older sub-cohort (S) involves uranium miners began underground work from 1948–1959 and who worked for at least 4 years (Tomasek 2012). The newer sub-cohort (N) consists of miners who were employed in the central part of Bohemia (Příbram mines) from 1968–1988, when radiation protection measures had already been fully implemented (Placek, Tomasek et al. 1997, Tomasek 2012). The miners selected for this sub-cohort worked for at least 1 year. The cohort used in this dissertation includes Czech miners from 1953 onward.	French miners were defined from administrative files of CEA and COGEMA, the companies in charge of uranium extraction in France. The date of first employment as a uranium miner plus 1 year from January 1, 1946–December 31, 1999 at CEA or COGEMA, working at the surface or underground and with no restriction on the duration of exposures. The cohort used in this dissertation includes French miners from 1956– onward.
Follow-up	1965–1999 Beaverlodge exposures began in 1965 to the final shutdown of mine in June 1982. Follow-up of non-Beaverlodge radiation exposures continued to 1999 through the National Dose Registry. Follow-up starts from the later of the date of hire or the start of follow-up defined as 1 January 1965. Follow-up ends the earliest of the date of death, last date known alive, or 31 December, 1999.	1953–1999 Follow-up starts 4 years after first employment as a uranium miner in the Czech cohort. Follow-up ends the earliest of four dates: date of death, date of last follow-up, 85th birthday, or 31 December, 1999.	1956–1999 Follow-up starts 1 year after first employment as a uranium miner in the French cohort. Follow-up ends the earliest of four dates: date of death, date of last follow-up, 85th birthday, or 31 December, 1999.

Exposures			
	Beaverlodge Cohort	**Czech Cohort**	**French Cohort**
Exposures	Radon: Estimated (1954–1968) At Beaverlodge, both radon and RDP measurements started in 1954 and continued at increasing frequency throughout the life of the mine. The total number of radon measurements taken per workplace per year from 1954–1968 was generally less than 12, with an average of about 4 measurements per workplace per year. The radon concentration measurements were converted to radon decay progeny product concentrations (in WLMs) using equilibrium factors determined in 1954, 1956, 1959 and 1961 through paired measurements of radon concentrations and radon progeny. Prior to individual exposure assignment, annual individual exposures were estimated using the annual geometric mean (GM) radon progeny concentration underground and in the mill and time spent in the workplace. The annual individual exposures were recalculated for all personnel for whom no individual exposures were recorded during the operation of the mine. The annual mean for workers was calculated by summing over the Working Level measurements available for each type of workplace, the proportion of employees in each occupation, and the proportion of time spent in each type of workplace by employees in each occupation (AECB, 1996)[1] Radon: Measured (1966+) Personal exposures were assigned, starting with underground miners in November 1966 and expanding to cover all personnel in the 1970s. Gamma Ray Information on individual gamma-ray doses was available for all Beaverlodge cohort members. At Beaverlodge, short campaigns of personal and area monitoring with film badges took place in the 1950s, and starting in 1963 a sampling of workers wore film badges fulltime. This coverage was gradually increased through the 1970s. Personal gamma-ray doses were calculated from the average dose rates and time on the job and expressed in millisieverts (mSv) for each individual who had not been wearing a badge. The National Dose Registry also contains information on gamma-ray doses for uranium miners starting in 1981 (Health Canada 2008). Other exposures Many workers' personnel records indicated prior experience in other early Western Canadian mines, and	Radon: Estimated (1949–1967) (S study) Although this dissertation begins in 1953, extensive radon gas measurements were conducted since 1949 in nearly all shafts (Tomasek et al, 1994). Duplicate air samples were measured in ionization chambers, and results were adjusted for time since sampling. There were about 200 such measurements per year and shaft in the period 1949–1960 and more than 900 afterward. The coefficient of variation ranged from 14% to 5% during 1949–1967. The numbers of measurements in different working places were proportional to the numbers of miners working at these locations. The mean annual concentrations of radon gas in different shafts were converted to concentrations of radon progeny (in WLM) using equilibrium ratios of 0.7, 0.5 and 0.3 depending on the level of ventilation. These ratios were derived from data when mechanical ventilation was not operated for 1 month (Tomasek, 2013). Each miner's annual exposure to RDP was estimated combining measurement data with registered employment details, including duration of underground work in different shafts and job category. Missing exposure data were extrapolated. Measured (1968+) (N Study) Individual exposure data used personal dosimetric records, based on several thousand measurements per year and shaft. This provided direct RDP measurements in the ambient air available since 1968 (Placek et al., 1997). In some shafts, measurements were not available in the first few years of operation, and exposure data were extrapolated from later data. Other radon and RDP exposures In addition to uranium mines, some miners in both cohorts also worked in non-uranium mines. Their exposures (substantially lower than those in uranium miners) were extrapolated from measurements in the mid–1960s from non-uranium mines (Sevc & Cech, 1966). Such exposures were classified as ''estimated''. The estimation of individual exposure makes use of information on the job in each year and month worked. Non-hewer jobs (maintenance, support, technical and supervising underground workers) had about half the exposure of hewers (generally miners working at fore field or stopes, including drillers and muckers). The actual job exposure matrix was derived from data for the N study.	Radon exposures were estimated individually for each year of employment. Three periods are distinguished in the methods of exposure assessment. Estimated (1946–1955) In the first period, annual individual exposures were estimated retrospectively in 1981 by a group of experts. Assessment was from environmental measurements in the mine and on information about the place, period and type of job for each miner. Measured (1956–1982) In 1956, important changes in radiation protection, especially the introduction of mechanical ventilation in each mine, an increase in the number of ambient measurements in the mines, and the systematic control of individual exposures led to a sharp decrease in annual exposures. From 1956 to 1982, individual annual radon exposures were estimated prospectively from ambient measurements taken in the mines combined with a detailed occupational history, including information recorded monthly on job title and work site (Leuraud et al, 2011). Exposures for each miner was routinely recorded each month in files, using measurements of ambient radon gas concentration at work sites, time worked and type of job. Measured (1983+) Since 1983, individual radon exposure was determined from the potential alpha energy of RDP measured by individual dosimeters worn by each miner. In addition to these gas measurements, several hundred measurements of *potential α-particle energy concentrations* (PAEC) were also performed in different FR mining divisions and were used to derive the equilibrium factor.

[1] SENES Consultants Limited, An algorithm for estimating radon progeny exposures from underground employment at the Eldorado Beaverlodge Mine. Atomic Energy Control Board of Canada, Richmond Hill, ON, 1996

Exposures			
	Beaverlodge Cohort	**Czech Cohort**	**French Cohort**
	many obtained employment in other mines or other industries with potential radiation exposure after leaving Eldorado. The National Dose Registry collects and records radiation exposure and dose data for all exposed workers in Canada from 1951 (with some records going back to 1944). However, the National Dose Registry had no early records from Eldorado and no records for any of the other early Western Canadian mines. For workers with mining exposure history in early non-Eldorado Western Canadian mines, exposure levels based on Working Level data from the Beaverlodge mine were estimated. For all other non-Eldorado radiation exposures from 1951–1999, the nominal roll was linked to the National Dose Registry records.		

Outcomes			
	Beaverlodge Cohort	**Czech Cohort**	**French Cohort**
Vital Statistics	An internal linkage and manual un-duplication/update was initially conducted for the entire Eldorado cohort (19,855 individuals). The cohort was linked to the Historic Summary Tax File from 1984–2000 to confirm vital status up to the end of follow-up in 1999, and was then linked to the Canadian Mortality Database from 1940–1999 (cause of death only from 1950–1999). In total, vital status was obtained for 15,580 (78.5%) of the Eldorado cohort. The 4,307 (21.8%) of individuals who could not be linked to the Historic Summary Tax File or the Canadian Mortality Database had their termination date at work as the last date alive. Further data processing led to exclusions of 2,195 (11.0%) records. The final cohort for mortality analysis consisted of 17,660 subjects (88.9% of the original cohort), of which 10,050 were Beaverlodge workers.	Information on vital status was obtained from the files of the Czech Population Registry at the Ministry of the Interior, the Social Security Office, and local administrative records.	Vital status of each miner was obtained from the French national vital status registry and recorded through the end of 1999 in one of the following categories: alive, dead, alive at 85 years, and lost to follow-up.
Mortality	The nominal roll file was linked to the Canadian Mortality Database from 1940–1999 via probabilistic record linkage (Howe, 1998). This database contains records of all deaths registered in Canada by all provinces and territories and those voluntarily reported deaths of Canadian residents in the United States. From 1940–1949 the Canadian Mortality Database only provides fact of death. This information was used for death clearances from 1940–1949, and deceased subjects were eliminated from further analysis. The Canadian Mortality Database has cause of death information since 1950, is considered to be complete and accurate, and is routinely used to ascertain mortality in a number of cohort studies (Howe, 1998).	Before 1982, causes of death were obtained from local death registries and since 1982 from the Institute of Health Information and Statistics of the Czech Republic (Tomasek 2013) Causes of death were obtained for 99% of the deaths. Miners of Slovak origin who moved back to Slovakia were followed up by the corresponding Slovak institutions.	Information on causes of death was collected from two complementary sources, depending on the period. From 1946–1967, causes of death were collected through an active search by the occupational medical department of COGEMA since national level information was not available in France. From 1968–1999, causes of death on came from a standardized anonymous linkage procedure with the French national mortality database that gathers information from death certificates in France. The COGEMA occupational medical department also served as a supplementary source of information for deaths after 1968 when the French national mortality data were missing or uninformative.
Outcomes	The underlying causes of death were recoded from the original International Classification of Disease (ICD) code in use at the time of death to ICD9 (WHO, 1998)	All causes of death were coded according to the ICD8 before 1978 and ICD9 afterward. Lung cancers were primary cancers (ICD8 and 9, 162) according to death certificates.	All causes of death were coded according to the ICD8 and ICD9. All results are presented according to ICD9.

Appendix B: Review of Potential Confounding Factors

Confounding risk factors are especially relevant to the radon-lung cancer mortality relationship at low radon exposures and low exposure rates since at these low levels, the radon-lung cancer mortality risk relationship is possibly at the limit detectable by current epidemiological methods (Rothman 2002, Rothman, Greenland et al. 2008). Any bias in the risk estimates due to confounding will have a greater impact on risk estimates at low radon exposures compared to high radon exposures, as seen in the past (Rothman 2002, Rothman, Greenland et al. 2008). Important potential confounding factors on the radon-lung cancer mortality relationship include tobacco smoking and residential radon exposure, other sources of occupational radiation, and other mine specific hazards. These are discussed below and summarized in Table B1.

Potential confounding effects of other occupational radiation exposures available from the uranium mine cohorts

Uranium miners are exposed to sources of ionizing radiation other than radon, including long-lived alpha (α) emitting radionuclides (LLR) present in the uranium ore dust, and external penetrating gamma (γ) radiation from radionuclides present in the mining environment (Duport 2002). These other sources of radiation could potentially confound the radon-lung cancer mortality relationship.

External gamma radiation exposure is known to be a statistically significant risk factor for lung cancer mortality from analyses on the Japanese atomic bomb survivors (Preston, Shimizu et al. 2003) for doses and dose rates much higher than those at uranium mines.

Currently, only a few cohorts of uranium miners (i.e., Beaverlodge, French, German, and Ontario) have sufficient accompanying data to take these additional radiation exposures into

account. External gamma radiation was available in the Beaverlodge cohort but it was not incorporated into the joint analysis because no information on external gamma radiation or LLR exposure was provided in the Czech and French cohorts for this dissertation. We reviewed the potential confounding effects of these radiation sources using findings from the published literature on uranium miners.

In the Eldorado study, which included Beaverlodge workers, RDP exposures and γ-ray doses were not correlated (Pearson's r = 0.18). No relationship between γ-rays and lung cancer incidence and mortality was found. Gamma radiation did not significantly add to the fit of the model for the background risk of lung cancer mortality or incidence ($P = 0.88$, $P = 0.84$, respectively). Similarly, there was no statistically significant evidence of any association between γ-ray doses and risk of any other cancers or any other causes of death. However, the mean γ-ray dose of workers was fairly low (25.6 mSv, SD = 39.4 for male Beaverlodge workers), so it is possible that the study lacked the statistical power to detect an effect (Lane, Frost et al. 2010).

Mortality risks associated with exposure to radon, external γ-rays and LLR were investigated in the French post-55 sub-cohort of uranium miners, since recording of dosimetry for γ-rays and LLR began in 1956. Cumulative exposures between radon and external γ-ray dose (r = 0.80; $P < 0.001$) and between radon and LLR (r = 0.74; $P < 0.001$) were highly correlated. A significant exposure-risk relationship was observed between lung cancer mortality and cumulative external γ-ray dose with regression in both the external (ERR/100 mSv = 0.80; 95% CI: 0.21–2.03) and internal (ERR/100 mSv = 0.72; 95% CI: 0.15–2.03) models. A borderline positive relationship between lung cancer mortality and cumulative LLR exposure reported was also found in both external comparison (ERR/100 Bq h/m^3 = 0.025;

95% CI: 0.003–0.067) and internal comparison (ERR/100 Bq h/m^3 = 0.025; 95% CI: 0.002–0.070) analyses. These results suggested an association between lung cancer and exposure to γ-ray and LLR; however, the authors cautioned that this may be due to the correlation between the different types of exposure and radon (Vacquier, Rage et al. 2011).

Further work has assessed the risk of lung cancer mortality among the French uranium miners associated with the annual weighted *absorbed lung dose* from radon gas, radon progeny and LLR in the uranium ore dust, as well as the external γ-ray dose (Rage, Vacquier et al. 2012). The mean absorbed lung dose due to alpha-particle and low-linear energy transfer (low-LET) radiation (mainly γ-rays, but also β-particle radiation) was 78 mGy and 56 mGy, respectively. Alpha-particles accounted for 58% of the absorbed lung dose and radon progeny accounted for 97% (76 mGy) of the α-particle absorbed dose. A significant excess relative risk of lung cancer death was associated with the total absorbed lung dose (ERR/Gy = 2.9; 95% CI: 0.8–7.5) and the α-particle absorbed dose (ERR/Gy = 4.5; 95% CI: 1.3–10.9). The ERR/Gy associated with radon progeny (ERR/Gy = 4.6; 95% CI: 1.3–11.2) was very close to that associated with the α-particle dose. Radon gas (1.9%) and LLR (1.3%), contributed minimally to the absorbed lung dose, resulting in imprecise risk coefficients with very wide confidence intervals. The ERR/Gy associated with external γ-ray dose was also limited because of the strong correlation with the α-particle component of the dose.

An updated mortality analyses in the French post-55 sub-cohort found that radon exposure was statistically significant for lung cancer (ERR/100 WLM = 2.42; 95% CI: 0.90–5.14, $P < 0.001$). A significant ERR due to cumulative external γ-ray exposure was also reported for lung cancer (ERR/100 mGy = 0.74; 95% CI: 0.23–1.73, $P < 0.001$), and ERR due to cumulative LLR exposure was also significant (ERR/100 kBq h/m^3 = 32.18; 95% CI: 9.16–

72.56, P = 0.002). However, the very large confidence intervals require that the latter be interpreted with caution (Rage, Caer-Lorho et al. 2014).

In the Czech Republic, exposures to radon progeny, external gamma radiation and LLR were only available from 2000–2012 in one uranium mine (Rožná), which has used ALGADE personal dosimeters for individual monitoring since 1998 (Sabol, Jurda et al. 2011, Marusiakova, Gregor et al. 2011, Otahal, Burian et al. 2014). Only the evaluation of exposures, not exposure-response relationship, was assessed. Also, this time period was after the follow-up of the Czech cohort used in this dissertation.

In the German Wismut uranium miners, the potential confounding effects of external γ-ray dose and LLR exposure were found to have only minor confounding influences on the ERR/WLM of lung cancer mortality. The central ERR/WLM = 0.0059 was not influenced to any notable degree by the inclusion of these exposures (i.e., the model-to-model variation in the radon ERR/WLM; the β_w central estimate ranged from 0.0055 to 0.0060) (Walsh, Tschense et al. 2010).

Mortality from cancer due to internal and external radiation exposure was further assessed in male German uranium millers (Kreuzer, Dufey et al. 2014). Mean cumulative exposure to long-lived radionuclides from uranium ore dust and external gamma radiation were 3.9 kBq h/m^3 (max = 132 kBq h/m^3) and 26 mSv (max = 667 mSv). A statistically significant relationship between cumulative radon exposure and lung cancer mortality (ERR/100 WLM = 3.39; 95% CI: -0.01–6.78; P = 0.05), was found. For external gamma radiation, an excess of mortality of solid cancers (ERR/Sv = 1.86; 95% CI: -0.08–3.80; P = 0.06), primarily due to stomach cancer (ERR/Sv = 10.0; 95% CI: -2.6–22.6; P = 0.12)

and lung cancer (ERR/Sv = 2.55; 95% CI: -0.97–6.07; P = 0.16) was present but was not statistically significant. No increase in risk of lung cancer mortality in relation to LLR was observed (ERR/100 kBq h/m^3 = -0.61; 95% CI: -1.42–0.19, P = 0.13).

These studies suggest that LLR has a minimum confounding effect on the radon-lung cancer mortality relationship; especially since it contributed minimally to the absorbed lung dose (Rage, Vacquier et al. 2012). However, the confounding effect of external γ-ray exposure is less clear, particularly in the French post-55 sub-cohort. None-the-less, the risk of lung cancer associated with cumulative radon exposure remained significant after taking exposure to γ-ray and LLR into account. Most importantly, alpha particles represented 58% of the absorbed lung dose and radon progeny accounted for 97% the alpha (α) particle absorbed dose to the lung(Rage, Vacquier et al. 2012)

Potential confounding effects of non-radiological occupational hazards in the mining environment

Uranium miners may also be exposed to arsenic and silica depending on the mineral content of the ore. They may also be exposed to diesel exhaust from mechanical equipment used in the mines, or other occupational hazards before/after working in a uranium mine.

Arsenic

The International Agency for Research on Cancer (IARC) has recently classified arsenic and inorganic arsenic compounds as carcinogenic to humans (IARC 2012). Arsenic has been studied predominantly in the Chinese tin miners (Chen, Chen 2002), and the German (Walsh, Tschense et al. 2010, Walsh, Dufey et al. 2010) and Ontario uranium miners (Kusiak, Ritchie et al. 1993) since these mines had high arsenic content.

Arsenic was not an occupational concern at the Beaverlodge mine and was unlikely an issue at any other operating mine in Saskatchewan [Mr. Stan Frost, personal communication, 2015-02-11]. No arsenic exposures were available in French uranium mines since it was not an exposure of concern (Leuraud, Schnelzer et al. 2011). In the Czech cohort, men who spent more than 20% of their employment at the Jáchymov mine had clear evidence of a higher risk of lung cancer (ERR/100 WLM = 1.8; 95% CI: 1.3–3.0) compared to other miners (ERR/100 WLM = 1.4; 95% CI: 0.5–3.5). Precise estimates of the men's arsenic exposure were not available; instead, cumulative arsenic exposures were estimated at termination of employment. Arsenic levels were known to be much greater in Jáchymov than in other mines, mean percentage of arsenic in dust 0.5% to 7.1% (Tomasek, Swerdlow et al. 1994, Tomasek, Darby 1995, Tomasek, Darby et al. 1994). However, the radon-lung cancer mortality risk relationship persisted after adjustment for arsenic estimates through stratification (Tomasek, Darby et al. 1994). Any potential confounding effects of arsenic is limited to Jáchymov miners first hired from 1953–1959, since those from 1948–1952 were excluded from the cohort.

Silica

A recent review by the International Agency for Research on Cancer Working Group concluded there is sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung (IARC 2012). Crystalline silica (quartz) has been studied predominantly in the Chinese tin miners (Chen, Zhuang et al. 2001, Chen, Hnizdo et al. 2005, Harrison, Chen et al. 2005), the Swedish iron ore miners (Jonsson, Bergdahl et al. 2010, Bergdahl, Jonsson et al. 2010), and the Colorado-Plateau (Schubauer-Berigan, Daniels et al.

2009), Ontario (Kusiak, Ritchie et al. 1993) and German uranium miners (Walsh, Grosche et al. 2014) since these mines had high quartz contents. Detailed analyses within the German cohort showed no major confounding by arsenic dust, fine dust, or silica dust on the radon-related lung cancer risk (Walsh, Tschense et al. 2010, Walsh, Dufey et al. 2010).

Silica levels were monitored at Beaverlodge but levels were very low and not an occupational concern. Silica is not an occupational concern at other Saskatchewan uranium mines (i.e., Rabbit Lake, McArthur River mines) where miners may have worked after leaving Beaverlodge [Mr. Stan Frost, personal communication, 2015-02-11]. There was no information on silica exposure among Czech uranium miners, and there were only trance amounts of chromium, nickel, and cobalt in the mine dust (Tomasek, Swerdlow et al. 1994, Tomasek, Darby 1995, Tomasek, Darby et al. 1994).

A statistically significant excess of silicosis mortality (N = 23, SMR = 7.1; 95% CI: 4.51−10.69) was found in the French cohort with follow-up from 1946–1999 (Vacquier, Caer et al. 2008). However, the radon-lung cancer mortality relationship (ERR/WLM = 0.011; 95% CI: 0.003−0.025) persisted, after adjustment for silicotic status, a proxy to crystalline silica exposure, (ERR/WLM = 0.007; 95% CI: 0.001−0.021) in a nested case-control study of French uranium miners (Amabile, Leuraud et al. 2009).

Diesel exhaust

The International Agency for Research on Cancer (IARC) has recently reviewed diesel engine exhaust and concluded that there is sufficient evidence in humans for the carcinogenicity of diesel engine exhaust, in particular cancer of the lung and cancer of the urinary bladder (IARC 2013).

Following the IARC's determination, the relationship between diesel emissions and lung cancer was reviewed and evaluated by the Health Effects Institute Diesel Epidemiology Panel (HEI Diesel Epidemiology Panel 2015). They evaluated the evidence of the lung cancer risk of diesel exhaust among studies of truckers (Garshick, Laden et al. 2012), and underground non-metal mines in the United States (Attfield, Schleiff et al. 2012, Silverman, Samanic et al. 2012, Garshick, Laden et al. 2012), which played a central role in IARC 's decision. The Panel concluded that the studies met high standards of scientific research and could be useful for estimating lung cancer risks due to diesel engine exhaust exposures in older diesel engines (HEI Diesel Epidemiology Panel 2015).

Minimal information on diesel exhaust among radon exposed miners is published. However, the increased risk of lung cancer in Swedish iron ore miners could not be explained by diesel exhaust exposure (Kusiak, Ritchie et al. 1993, Bergdahl, Jonsson et al. 2010). No exposure information on diesel exhaust was available in the Beaverlodge, Czech or French cohorts. Diesel was introduced into the Beaverlodge mine in the last few years prior it's shut down in 1982 [Mr. Stan Frost, personal communication, 2015-02-11]. No measurements for diesel exhaust were available in the French mines since diesel engines were not introduced until the mid-1970s. The Czech uranium mines only used electric powered equipment.

Other hazardous exposures

Finally, uranium miners could work with other hazardous exposures before/after uranium mining. Since mean duration of employment at a uranium mine is short, hazardous exposures from other employment could have a considerable influence on lung cancer risk. Confounding effects of other gold and hard rock mining experience did not contribute to the radon-lung cancer mortality relationship in a nested case-control study of Beaverlodge

miners (L'Abbé, Howe et al. 1991). There was no information on uranium miners' other hazardous exposures.

Potential confounding factors from nested case-control study subset of the cohorts only (tobacco smoking and residential radon)

The main cause of lung cancer is cigarette smoking. Smoking is estimated to be related to more than 85% of lung cancer cases in Canada. Similarly, the longer a person smokes and the more cigarettes smoked each day, the more the risk increases (Canadian Cancer Society, 2016; PHAC, 2015-07-03).

A meta-analysis of tobacco smoking and lung cancer found the pooled relative risk of lung cancer among current smokers was RR = 8.96 (95% CI: 6.73–12.11) and among former smokers RR = 3.85 (95% CI: 2.77–5.34). Similarly, the risk of lung cancer increased by 7% for each additional cigarette smoked per day; RR = 1.07 (95% CI: 1.06–1.08) (Gandini, Botteri et al. 2008). Thus, the impact of tobacco smoking among uranium miners may be a very important confounding factor; especially at low cumulative radon exposure.

Uranium miners traditionally have a very high prevalence of tobacco smokers (Bruske-Hohlfeld, Rosario et al. 2006, L'Abbé, Howe et al. 1991, Leuraud, Billon et al. 2007, Hunter, Muirhead et al. 2013, Leuraud, Schnelzer et al. 2011, Tomasek 2013, Tomasek 2011, Amabile, Leuraud et al. 2009, Kreuzer, Brachner et al. 2002). Even today, tobacco smoking is known to be high among modern uranium miners. A survey in Saskatchewan, Canada found that about 70% of Rabbit Lake miners smoked at some time (CNSC 2003).

Smoking information on all miners is only available in the updated cohort studies of the Colorado Plateau and Newfoundland fluorspar miners (Schubauer-Berigan, Daniels et al. 2009, Villeneuve, Morrison et al. 2007). However, their demographic and exposure

characteristics were not representative of the Czech, French and Beaverlodge miners used in the primary dataset.

The Colorado Plateau miners had very high cumulative radon exposures (mean = 794 WLM, SD = 1,090) based largely on exposure estimates made in the early 1970s. The referent exposure category was < 120 WLM, which was greater than the < 100 WLM focus of the primary analysis. About 20% of miners were Navajo first nations. Over 84% of Caucasian but only 45% of Navajo miners were current or former smokers. Similarly, among current smokers, Caucasian miners (78%) were much more likely than Navajo miners (10%) to smoke at least a pack a day.

The underground Newfoundland fluorspar miners also had very high cumulative radon exposures (mean = 378 WLM over an average of 5.5 y of exposure) based largely on exposure estimates made in 1960 from a review of historical work conditions of the mine and mine architecture. The referent exposure category was < 200 WLM which was greater than the < 100 WLM focus of the primary analysis. There were only eight lung cancer deaths (N = 8) among never smokers, so the referent group was those who smoked < 15 cigarettes per day.

Information on the relationship between radon and tobacco smoking on lung cancer is also available from nested case-control studies (L'Abbé, Howe et al. 1991, Leuraud, Schnelzer et al. 2011, Tomasek 2011, Tomasek 2013, Hunter, Muirhead et al. 2013, Amabile, Leuraud et al. 2009, Bijwaard, Dekkers et al. 2011, Schnelzer, Hammer et al. 2010, Leuraud, Billon et al. 2007, Bruske-Hohlfeld, Rosario et al. 2006) and recent indirect adjustment methods for confounding variables (Walsh, Tschense et al. 2010, van Dillen, Dekkers et al. 2016,

Bijwaard, Dekkers et al. 2011, van Dillen, Dekkers et al. 2011, van Dillen, Dekkers et al. 2010)

The results of these studies confirm that a linear excess relative risk model for the radon-lung cancer mortality relationship persists even when smoking is adjusted for. These findings suggest that results from studies without smoking information are still valid and that smoking does not act as a major confounder on the radon-lung cancer mortality risk relationship in studies of uranium miners.

The relative risks from combined effects of radon and smoking are substantially lower than the risk derived from the multiplicative model, with arguments in favour of sub-multiplicative interaction between radon and tobacco smoking (Schubauer-Berigan, Daniels et al. 2009, Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2013, Tomasek 2013, Tomasek 2011, Leuraud, Billon et al. 2007).

Findings also reflect mainly the risk among smokers since the prevalence of ever smokers ranged from about 60% to 80% of the uranium miner population. For example, in Kusiak et al., 1993, about 80 % of the Ontario uranium miners with smoking information were regular cigarette smokers. However, no association between the proportion of smokers and cumulative exposure to radon progeny could be detected, making it improbable that smoking contributed to the increased incidence of lung cancer.

Finally, the excess relative risks of lung cancer per radon exposure (WLM) were greater for non-smokers compared to current or ex-smokers, likely reflecting differences in lung morphometry and clearance (Amabile, Leuraud et al. 2009, Schnelzer, Hammer et al. 2010, Hunter, Muirhead et al. 2013, Bijwaard, Dekkers et al. 2011, Tomasek 2011).

Residential radon

Residential radon may also potentially confound the relationship between occupational radon exposure and lung cancer since miners will also be exposed to radon in their homes. No studies are currently available to assess the potential confounding effect of residential radon on the occupational radon-lung cancer relationship. However, residential radon is related to socio-economic status (SES), which may also be related to occupational radon exposures. People with higher SES who live in single family homes have higher residential radon exposures compared to people of lower SES who live in multiple family dwellings (AGIR 2009).

Occupational and residential radon risk was assessed in two Czech nested case-control studies. However, the contribution of residential exposure on lung cancer risk among miners exposed to occupational radon was not assessed. The evidence of an effect from residential radon is generally more difficult to assess because of lower exposures and uncertainties in exposure estimates (Tomasek 2013).

Table B1 Potential confounding factors in the Beaverlodge, Czech and French cohorts of uranium miners

Risk Factor	Beaverlodge	Czech	French
Potential confounding factors from the uranium miner cohorts			
Gamma (γ) radiation	√ Short campaigns of personal and area monitoring with film badges in 1950s. In 1963 a sample of workers wore film badges fulltime; coverage was increased through the 1970s. The National Dose Registry (NDR) collected and recorded radiation dose for all exposed workers in Canada from 1951; information on gamma-ray doses for miners started in 1981 (Lane, Frost et al. 2010).	√ (prior to 1966 statistical model, 1966 onward film badges) Rozna ALGADE dosimeters since 1998 for gamma (Otahal, Burian et al. 2014, Marusiakova, Gregor et al. 2011, Sabol, Jurda et al. 2011)	√ (1956−1985 film badge CEA PSI type, 1986 TLDs) (Vacquier, Rage et al. 2011, Rage, Vacquier et al. 2012, Rage, Caer-Lorho et al. 2014)
Long − lived Radionuclides	x	√ Rozna ALGADE dosimeters since 1998 for LLR (Otahal, Burian et al. 2014, Marusiakova, Gregor et al. 2011, Sabol, Jurda et al. 2011)	√ (Vacquier, Rage et al. 2011, Rage, Vacquier et al. 2012, Rage, Caer-Lorho et al. 2014)
Potential confounding factors from a nested case-control study subset of the cohorts only			
Tobacco smoking	√ (nested case-control) (L'Abbé, Howe et al. 1991, CNSC 2003)	√ (nested case-control) (Leuraud, Schnelzer et al. 2011, Tomasek 2002, Tomasek 2011, Tomasek 2013, Hunter, Muirhead et al. 2013)	√ (nested case-control) (Leuraud, Schnelzer et al. 2011, Amabile, Leuraud et al. 2009, Hunter, Muirhead et al. 2013, Leuraud, Billon et al. 2007)
Residential Radon	√(Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005, Axelson, Steenland 1988)	√ (Tomasek 2013) residential radon analyzed separately in a residential cohort, not among miners	√ (Tomasek 2013, Darby, Hill et al. 2005, Darby, Hill et al. 2006)
Potential confounding information from external sources and studies (i.e., not from the worker cohorts at all).			
Arsenic	x	(Tomasek, Darby 1995, Tomasek, Swerdlow et al. 1994, Tomasek, Darby et al. 1994). There were only "trace amounts" of chromium, nickel, and cobalt in the mine dust." Arsenic levels were much greater in Jáchymov (mean percentage of arsenic in the dust 0.5%, maximum 7.1%)	x
Silica	x	x	√ (only some information on the silicotic status) (Amabile, Leuraud et al. 2009)
Diesel exhaust	x(Krewski, Lubin et al. 2006, Krewski, Lubin et al. 2005, Axelson, Steenland 1988)	Not exposed (electric power). All artificial ventilation was carried out with electric motors; no diesel engines were used.	No measurements available; only know mechanization with diesel engine began in mid − 1970s.

√ some information on the risk factor was available within the cohort.
x no information on the risk factor was available within the cohort.

Appendix C: Review of Potential Effect Modifiers

Lubin and colleagues' joint analysis of 11 studies of radon-exposed miners and the BEIR VI Committee all supported the exposure-age-concentration and exposure-age-duration models to reflect the impact of effect modifiers on the radon-lung cancer mortality relationship. Cumulative radon exposures received in different time since exposure windows, attained age, and either the concentration (exposure rate) or the duration of radon exposure were significant effect modifiers in the radon-lung cancer mortality relationship. The risk of lung cancer decreased with increasing time since exposure, attained age, and exposure rate. However, when the data was restricted to low cumulative exposures, or low expose rates, there was a diminution of the exposure rate effect (National Research Council 1999, Lubin, Boice et al. 1995a, Lubin, Boice et al. 1994, Lubin, Boice et al. 1995b).

Historical cohorts of radon-exposed miners, joint analyses of the European cohorts of uranium miners, and joint nested case-control studies of the European cohorts of uranium miners, especially those restricted to low cumulative radon exposures, have been updated. All find a statistically significant increased risk of lung cancer associated with cumulative radon exposure. Alternatives to the BEIR VI models have also expanded the understanding of effect modifiers on the radon-lung cancer mortality relationship at low cumulative radon exposures.

A joint analysis of French (1956–1994) and Czech (1952–1995) uranium miners assessed the radon-lung cancer mortality relationship focusing on low levels of exposures, protracted over a long time period, with good quality individual exposure estimates. Substantial improvements in the quality of exposure information over time, enabled researchers to partition exposures into those "estimated" (i.e., prior to 1956 for France, prior to 1952 for

Czech miners) and those with relatively good quality “measurements”. For age at exposure of 30 years, and 20 years since exposure, the ERR/WLM decreased by approximately 50% for each ten-year increase in age at exposure and time since exposure. These were the most important effect modifiers. The quality of exposure estimates was an important factor that substantially influenced results. The risk of lung cancer was greater among “measured” exposures, which reflected increased accuracy of measured exposures compared to the uncertainty in “estimated” exposures. No inverse exposure rate effect below 4 WL was observed. Results were consistent with estimates of the BEIR VI exposure-age-concentration model at an exposure rate below 0.5 WL (Tomasek, Rogel et al. 2008).

Follow-up of Czech uranium miners (1952–2010) found the radon-lung cancer mortality relationship was significantly modified by time since exposure, age at exposure and exposure rate using exposure windows. Risk of lung cancer mortality decreased with increasing time since exposure and age at exposure. In the final model, the inverse exposure rate effect was observed for high exposure rates > 7 WL with ERR/WLM reduced to 31%. The ERR/WLM decreases to 32% and 9% in periods 20–29 and 30+ years since exposure in comparison to the period of 5–19 years since exposure. Simultaneously, the ERR/WLM decreases with age at exposure by 63% and 49% at ages 30–39 and 40+ years in comparison to age at exposure < 30 years (Tomasek 2012).

Time since exposure; exposure rate and attained age were important effect modifiers of the radon-lung cancer mortality relationship in the Canadian Eldorado[2] uranium miners (1950–1999). The excess relative risk decreased monotonically with increasing time since exposure

[2] The Canadian Eldorado cohort study (1950–1999) includes three main sub-cohorts: Port Radium uranium miners from the Northwest Territories, the Beaverlodge uranium miners from northern Saskatchewan, and the Port Hope radium and uranium refining and processing workers from Ontario.

from 5–14 years ($P < 0.001$), excess relative risks decreasing monotonically with increasing exposure rate from 0.5 WL ($P = 0.001$). Finally, adding attained age also improved the fit but not significantly ($P = 0.06$); risk decreased with increasing age compared to age 55 years. These findings were in agreement with the BEIR VI exposure-age-concentration model (Lane, Frost et al. 2010).

Follow-up of Newfoundland fluorspar miners (1950–2001) found the radon-lung cancer mortality ERR/WLMs decreased significantly with increasing attained age, and time since last exposure ($P < 0.001$). A strong exposure rate effect was also observed ($P < 0.01$). However, no statistically significant differences were observed for either age at first exposure ($P = 0.30$), or year first employed (< 1960, ≥ 1960, the year when mechanical ventilation was introduced in the mines) ($P = 0.27$). However, the few lung cancer deaths prevented the joint modelling of these factors; many of which were correlated with each other. An analysis of the exposure rate effect estimated relative risks associated with duration of exposure within cumulative radon exposure strata (< 200, 200−900, ≥ 900 WLM). Within each exposure category, the relative risks increased with a longer duration of exposure. The linear test for trend was statistically significant in each cumulative WLM category ($P < 0.05$), which suggests the inverse exposure rate effect persists for cumulative exposures < 200 WLM (Villeneuve, Morrison et al. 2007).

An update of the French uranium miners (1946–1999) assessed several modifying factors on the exposure-risk. The most significant modifier was the period of exposure ($P = 0.001$). The ERR/WLM was ten times higher for exposure received after 1956 compared to before 1956. The ERR/WLM decreased with time since exposure ($P = 0.04$); especially after 25 years. An inverse exposure rate effect was observed with duration of exposure ($P = 0.06$) and exposure

rate (P = 0.001), especially for exposure rates > 1 WL/year. Age at exposure was not a significant modifying effect (P = 0.20). Physical activity significant modified the exposure-risk relationship (P = 0.01), the ERR/WLM being higher for ‘‘hard physical activity’’. Finally, a significant modifying effect of mine type (P = 0.02), was observed, with higher ERR/WLM for underground verses open pit miners. Mine location was not a significantly modifying effect (P = 0.36) (Vacquier, Rogel et al. 2009).

The authors of the updated German study of Wismut uranium miners (1946–2003) developed the Wismut model (Walsh, Tschense et al. 2010, Walsh, Dufey et al. 2010). This continuous model is linear in cumulative radon exposure and has exponential effect modifiers that depend on the whole range of age at median exposure, time since median exposure, and radon exposure rate. The Wismut model produces very similar central risk estimates to that using the BEIR VI Exposure-Age-Concentration model. In the German miners, the central estimate of ERR/WLM = 0.0054 (95% CI: 0.0040–0.0068) for age at median exposure of 30 years, time since median exposure of 20 years, and mean exposure rate of 3 WL. The ERR decreased by 5% for each unit of exposure rate increase, by 28% with each decade increase in age at median exposure, and by 51% with each decade increase in time since median exposure. The method of radon exposure (i.e., estimated, measured) was not an important effect modifier. Finally, the inverse exposure rate effect was investigated applying different exposure cut-off values. The exposure rate effect disappeared at 100 WLM, which is consistent with the lack of an inverse exposure rate effect for data restricted to exposures below 100 WLM (Lubin, Boice et al. 1995, National Research Council 1999). However, the ERR/WLM was not modified by duration of exposure in recent German uranium miners (Kreuzer, Schnelzer et al. 2010, Grosche, Kreuzer et al. 2006). Most

recently, the radon-lung cancer mortality risk relationship at low radon exposure rates was investigated in the 1960– sub-cohort of German uranium miners A cut off of radon exposures to < 100 or 50 WLM resulted in a significant ERR/WLM of 0.016 or 0.013, respectively. However, the ERR/WLM did not differ by time since or age at median exposure or exposure rate (Kreuzer, Fenske et al. 2015).

A joint analysis of the Czech, French and German nested case-control studies of lung cancer found time since exposure had a major effect on the radon-lung cancer mortality relationship among radon-exposed miners with exposures restricted below 300 WLM. The risk of lung cancer death decreased with increasing attained age ($P = 0.012$) and average annual exposure ($P = 0.005$) (adjusted for smoking). Duration of exposure did modify the exposure-risk relationship ($P > 0.5$). Period of exposure affected the exposure–risk relationship; the ERR/WLM estimated among miners employed in the early years (< 1953 Czech, < 1956 French, German) was significantly lower than that estimated among miners first employed more recently ($P = 0.006$). Time since exposure was a major modifier of the radon-lung cancer mortality risk. The ERR/WLM was six times higher for more recent exposures (5–24 years) than for more distant exposures ($P < 0.001$). The joint analysis of the European nested case-control studies of lung cancer was restricted to cumulative radon exposures < 300 WLM. Time since exposure and attained age remained significant effect modifiers; ($P < 0.001$, $P = 0.02$). However, country, exposure rate and smoking status were no longer significant effect modifiers ($P \geq 0.50$) (Leuraud, Schnelzer et al. 2011, Hunter, Muirhead et al. 2015).

Effect modifiers were not assessed in the Colorado, New Mexico or Swedish miner cohorts (Boice, Cohen et al. 2008, Jonsson, Bergdahl et al. 2010, Schubauer-Berigan, Daniels et al. 2009).

Appendix D: Radon Exposures and Non-Lung Cancers and Other Causes of Deaths

Publication	Cohort	Exposure	Outcome	Risk Estimate
Rericha et al, 2006	Příbram, Czech Republic (Case-cohort)	Radon (WLM) RR comparing high (110 WLM; 80th percentile) to low radon exposure (3 WLM; 20th percentile)	All leukemia incidence	RR = 1.75 (95% CI: 1.10–2.78; *P* = 0.014)
			CLL incidence	RR = 1.98 (95% CI: 1.10–3.59; *P* = 0.016)
			Myeloid leukemia incidence	Elevated but non-significant associations.
			Non-Hodgkin lymphoma incidence.	No associations were found.
			Multiple myeloma incidence	No associations were found.
Kreuzer et al, 2006	German	Radon (WLM)	Circulatory diseases mortality	ERR/100 WLM = 0.0006; 95% CI: -0.004–0.006
Villeneuve et al, 2007	Nfld. Fluorspar	Radon (WLM)	Coronary heart disease	There was no trend evident between cumulative exposure to radon and the relative risk of death (*P* = 0.63).
Kreuzer et al, 2008	German	Radon (WLM)	All extra-pulmonary cancer mortality	ERR/WLM=0.014%; 95% CI: 0.006–0.023%
Nusinovici et al, 2010	French	Radon (WLM)	Cerebrovascular diseases mortality	ERR/100 WLM = 0.49: 95% CI: 0.07–1.23
Lane et al, 2010	Eldorado	Radon (WLM)	Other cancers mortality	ERR/100 WLM =0.06; *P* = 0.51; n =113
			Leukemia mortality	ERR/100 WLM = 0.02; *P* = 0.81; n = 34
			Ischaemic heart disease mortality	ERR/100 WLM = - 0.01, *P* = 0.18; n = 1235
			Stroke mortality	ERR/100 WLM = - 0.04; *P* = 0.012; n = 244
			Other cardiovascular diseases mortality	ERR/100 WLM = - 0.02; *P* = 0.49; n = 317
			Respiratory disease mortality	ERR/100 WLM = 0.02; *P* = 0.59; n = 158
Kreuzer et al, 2010	German	Radon (WLM)	Extra-thoracic and trachea cancer mortality	ERR/WLM = 0.062%; 95% CI: 0.002– 0.121%
			Coronary heart diseases	No association found; ERR/WLM = 0.0003%
			Cerebrovascular diseases	No association found; ERR/WLM = 0.001%
Kulich et al, 2011	Příbram, Czech Republic (Case-	Relative risks comparing 180 WLM (90th percentile) of	All non-lung solid cancers incidence.	RR = 0.88 (95% CI: 0.73–1.04, n = 1020)
			All digestive cancers incidence.	RR = 0.87 (95% CI: 0.69–1.09, n = 561)
			Gallbladder cancer incidence.	RR = 2.39 (95% CI: 0.52–10.98, n = 13)

Publication	Cohort	Exposure	Outcome	Risk Estimate
	cohort)	cumulative lifetime radon exposure to 3 WLM (10th percentile)	Larynx cancer incidence.	RR = 0.79 (95% CI: 0.38–1.64, n =62)
			Malignant melanoma incidence.	RR = 2.92 (95% CI: 0.91–9.42, n = 23)
			Bladder cancer incidence	RR = 0.84 (95% CI: 0.43–1.65, n = 73)
			Kidney cancer incidence.	RR = 1.13 (95% CI: 0.62–2.04, n = 66)
Kreuzer et al, 2012	German	Absorbed dose α radiation (high LET)	Stomach cancer mortality	ERR/Gy = 22.5; 95% CI: -26.5–71.5
Walsh et al, 2012	German	Day worked underground	Prostate cancer mortality	ERR/day worked underground = -5.59 (95% CI: -9.81– -1.36) ×10(-5); (*P* = 0.0096)
Zablotska et al, 2012	Eldorado	Radon (WLM)	All malignant lymphoma mortality	ERR/100 WLM = 0.0 (n.e.) n = 49
			Multiple myeloma mortality	ERR/100 WLM = 0.04; 95% CI: < 0–1.07, n = 18
			All leukemia mortality	ERR/100 WLM = 0.02; 95% CI: < 0–0.46, n = 34
			All hematological cancers mortality	ERR/100 WLM = 0.02; 95% CI: < 0–0.23), n = 101
Dufey et al, 2013	German	Absorbed liver dose high LET radiation (mainly radon);	Liver cancer mortality	ERR/Gy = 48.3 (95% CI: -32.0–128.6, n = 159)
		Equivalent liver dose	Liver cancer mortality	ERR/Sv = 0.57 (95% CI: -0.69–1.82)
Kreuzer et al, 2013	German	Radon (WLM)	Non-malignant respiratory mortality	Cumulative radon exposure (mean = 280; max = 3224 WLM) was not related to death of any non-malignant respiratory.
Drubay et al, 2014	French & German	Radon (WLM), kidney equivalent dose	Kidney cancer mortality	No significant association with any occupational radiation exposure or kidney equivalent dose.
Rage et al, 2014	French	Radon (WLM)	Cerebrovascular disease mortality	(ERR/100 WLM = 0.41; 95% CI: 0.04–1.03)
Drubay et al, 2015	French (Nested case-control study)	Radon (WLM)	All circulatory diseases mortality	Hazard ratios: HR/100 WLM = 1.11 (95% CI: 1.01–1.22) The model was adjusted for circulatory disease risk factors (i.e., overweight, hypertension, diabetes, hypercholesterolemia and smoking status), HR/100WLM = 1.21 (95% CI: 0.54–2.75).
			Cerebrovascular disease mortality	HR/100 WLM = 1.25 (95% CI: 1.09–1.43)
Walsh et al, 2015	German	Radon (WLM)	Cancers of the extra-thoracic airways mortality	Not statistically related to occupational exposures.

Publication	Cohort	Exposure	Outcome	Risk Estimate
			All extra-pulmonary cancers mortality	Not statistically significantly related to occupational exposures.
			Cardiovascular diseases mortality	Not statistically significantly related to occupational exposures.
			Leukaemia mortality	No associations between and occupational doses of ionising radiation were found.
Kreuzer et al, 2016	German	Red bone-marrow dose of high LET (mainly radon) radiation.	Non-CLL mortality	ERR/Gy = 16.65; 95% CI: -1.13–46.75, n = 120
			Myeloid leukaemia mortality	ERR/Gy = 26.02; 95% CI: 2.55–68.99, n = 99
			CLL mortality	No association was found (n = 70).

Appendix E: Healthy Worker Survivor Bias

Health status has a major influence on hiring, job changes and job termination, creating a potential selection bias in occupational studies. This selection bias is comprised of two components (Arrighi, Hertz-Picciotto 1994) referred to as follows:

- healthy worker bias, and
- healthy worker survivor bias.

Healthy individuals have characteristics that make them more likely to get initially hired and remain employed. In contrast, the severely ill or chronically disabled are often less able to become and remain employed. There are also many health benefits of work, such as improved access to healthcare, routine disease screening, health insurance, physical activity and socialization (Arrighi, Hertz-Picciotto 1994, Picciotto, Hertz-Picciotto 2015).

The magnitude of this effect depends upon the occupation and disease. Workers of vigorous occupations, such as underground mining, are expected to be more physically fit. They also often have a lower mortality rate than workers with easier occupations or the unemployed (McMichael, Spirtas et al. 1974, McMichael 1976, Goldsmith 1975, Shah 2009, Breslow, Day 1987, Ogle 1885, Buckley, Keil et al. 2015).

Similarly, the effect appears to be greater for diseases with chronic morbidity (i.e., musculoskeletal, respiratory and cardiovascular diseases) compared to other diseases, such as cancer. For cancer, the effect is smaller for incidence than for mortality since those with a cancer diagnosis are likely to alter their employment status (i.e., reduce work hours, reduce work load, take sick leave/disability leave). The survival rate of the cancer may also impact the effect (Breslow, Day 1987). Time related factors (age at hire, age at risk), duration of

employment, socioeconomic status, and gender may also influence this effect (Shah 2009, Buckley, Keil et al. 2015).

The healthy worker effect produces lower mortality (or morbidity) rates for many causes of death among workers compared to the general population, so may mask real effects due to an occupational exposure (Breslow, Day 1987). Healthy hire bias exists in comparisons of workers with external reference populations. Since workers tend to be healthier than the general population, which includes those too sick or too disabled to work. Comparisons often reveal lower mortality (or morbidity) rates among workers. This bias will reduce the association between exposure and outcome by about 20–30%, so could lead one to conclude the exposure is protective or less harmful (Breslow, Day 1987, Shah 2009). Thus, mortality rates in the general population may be inappropriate for comparison with workers. This bias can be controlled by using an internal reference group of workers (Buckley, Keil et al. 2015).

Healthy worker survivor bias is a continuing selection process whereby workers with poorer health accrue less exposure (i.e., reduce their work hours, do less strenuous work, leave work, or retire prematurely) compared with their healthier counterparts. This bias results when comparing workers with long versus short term work durations. It is especially true for strenuous jobs, such as underground mining (Bjor, Damber et al. 2015, Buckley, Keil et al. 2015). If occupational data are not analyzed appropriately, the exposure may appear to be protective or less harmful (Buckley, Keil et al. 2015, Checkoway, Pearce et al. 2004, Steenland, Deddens et al. 1996).

Conceptualizing healthy worker survivor bias through causal diagrams can help identify relationships among variables and determine appropriate analytic methods (Greenland, Pearl

et al. 1999, Pearl 1995). Exposure lagging, restriction, adjusting for employment status, and the application of g-methods (Buckley, Keil et al. 2015) have been proposed to control healthy worker survivor bias.

In cohort studies, exposure lagging is an analytic method whereby exposure classification of person-time id determined by exposure status from before a given cut-off time (Checkoway, Pearce et al. 2004). Exposure lagging can be used to control bias due to exposure misclassification. This results when changes in job status are rooted in undetected, early stage disease. This may lead to lower exposure among those who are diagnosed shortly after a disease related change in jobs. Lagged analyses are appropriate when there is no causal relationship between the exposures during the lag period and the disease outcome (Gilbert 1982, Garshick, Laden et al. 2012). Cancer risk after radiation exposure has been shown to increase only after a minimum induction period of several years, depending on the type of cancer.

Induction time is the amount of time that must pass before some level of cumulative exposure would show as a detectable effect. The induction period begins only after exposure has triggered a physiological change / process, and that point also varies among individuals (Rothman, Greenland et al. 2008). The length of the induction period can be modelled by lumping raw data into categories of time since exposure. The time period yielding the highest risk represents the most appropriate period (Rothman 1981). Ideally, a study hypothesis could include a minimum induction time for effects based on causal principles, which in turn could form the basis for an appropriate lag time to be used in classifying individual experience.

Restriction refers to restricting the study cohort's inclusion criteria by factors that vary over time. For example, the cohort's inclusion criteria could require that everyone have survived for a specified period up to inclusion in the cohort. This approach assumes health related attrition from the workforce ceases after a period of employment (Buckley, Keil et al. 2015). However, there are problems with restricting workers by duration of employment. This strategy will guarantee that the study will miss effects among short term workers. For example, short term workers may be assigned more highly exposed jobs, they may include persons more susceptible to exposure effects, or they may quit early because of health effects. Because restrictions excludes short term workers, inference is limited to only a healthy subset of the population (Buckley, Keil et al. 2015, Rothman, Greenland et al. 2008).

Stratification is the analysis of exposure effects with strata of confounders, or as a weighted average of the effect measures across strata. Thus, healthy worker survivor bias can be conceptualized as a form of confounding by employment status (Buckley, Keil et al. 2015). Stratifying by employment status (Steenland, Stayner 1991) and including a term for active employment in a regression model for time varying exposures (Gilbert 1982) has been proposed as a control. This method can be problematic because long term workers tend to be healthier. Similarly, if exposure influences employment status, stratifying employment status (e.g., active employment status, employment duration) induces bias (Buckley, Keil et al. 2015).

Standardization refers to a process in which the outcome is summarized with a weighted average. Robins (1986) developed a set of approaches known as the g-methods which generalize standardization to complex longitudinal data (Robins 1986). These methods focus on potential outcomes, or outcomes that would be observed for an individual worker under a

particular exposure history. These methods of standardization are used when employment status is a time varying confounder affected by prior exposure. G-methods have only recently been applied to account for employment status of radon-exposed miners (Keil, Richardson et al. 2015, Bjor, Damber et al. 2015, Edwards, McGrath et al. 2014). These studies suggest that these new methods result in less biased risk estimates than standard methods (lagging, restriction, stratification). Although software is available, these methods require considerable analytical effort (Buckley, Keil et al. 2015).

9 References

AGIR, 2009. *Radon and public health. Report of the independent Advisory Group on Ionising Radiation.* Doc HPA, RCE-11. Chilton: Health Protection Agency.

ALAVANJA, M.C., BROWNSON, R.C., LUBIN, J.H., BERGER, E., CHANG, J. and BOICE, J.D., Jr, 1994. Residential radon exposure and lung cancer among nonsmoking women. *Journal of the National Cancer Institute,* **86**(24), pp. 1829-1837.

AMABILE, J.C., LEURAUD, K., VACQUIER, B., CAER-LORHO, S., ACKER, A. and LAURIER, D., 2009. Multifactorial study of the risk of lung cancer among French uranium miners: radon, smoking and silicosis. *Health physics,* **97**(6), pp. 613-621.

APPLEBAUM, K.M., MALLOY, E.J. and EISEN, E.A., 2007. Reducing healthy worker survivor bias by restricting date of hire in a cohort study of Vermont granite workers. *Occupational and environmental medicine,* **64**(10), pp. 681-687.

ARNSTEIN, A., 1913. On the so-called "Schneeberg Lung Cancer.". *Verhandl di deutsch path Gesellsch,* **16**, pp. 332-342.

ARRIGHI, H.M. and HERTZ-PICCIOTTO, I., 1994. The evolving concept of the healthy worker survivor effect. *Epidemiology,* **5**(2), pp. 189-196.

ATTFIELD, M.D., SCHLEIFF, P.L., LUBIN, J.H., BLAIR, A., STEWART, P.A., VERMEULEN, R., COBLE, J.B. and SILVERMAN, D.T., 2012. The Diesel Exhaust in Miners study: a cohort mortality study with emphasis on lung cancer. *Journal of the National Cancer Institute,* **104**(11), pp. 869-883.

AXELSON, O., 1978. Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health,* **4**, pp. 85-89.

AXELSON, O. and STEENLAND, K., 1988. Indirect methods of assessing the effects of tobacco use in occupational studies. *American Journal of Industrial Medicine,* **13**(1), pp. 105-118.

BALE, W.F., 1980. Memorandum to the files, March 14, 1951: Hazards associated with radon and thoron. *Health Phys,* **38**, pp. 1062-1066.

BERGDAHL, I.A., JONSSON, H., ERIKSSON, K., DAMBER, L. and JARVHOLM, B., 2010. Lung cancer and exposure to quartz and diesel exhaust in Swedish iron ore miners with concurrent exposure to radon. *Occupational and environmental medicine,* **67**(8), pp. 513-518.

BIJWAARD, H., DEKKERS, F. and VAN DILLEN, T., 2011. Modelling lung cancer due to radon and smoking in WISMUT miners: preliminary results. *Radiation Protection Dosimetry,* **143**(2-4), pp. 380-383.

BJOR, O., DAMBER, L., JONSSON, H. and NILSSON, T., 2015. A comparison between standard methods and structural nested modelling when bias from a healthy worker survivor effect is suspected: an iron-ore mining cohort study. *Occupational and environmental medicine,* **72**(7), pp. 536-542.

BLAIR, A., STEWART, P., LUBIN, J.H. and FORASTIERE, F., 2007. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. *American Journal of Industrial Medicine,* **50**(3), pp. 199-207.

BOICE, J.D., Jr, 1997. Radon, your home or mine? *Radiation research,* **147**(2), pp. 135-137.

BOICE, J.D.,Jr, COHEN, S.S., MUMMA, M.T., CHADDA, B. and BLOT, W.J., 2008. A cohort study of uranium millers and miners of Grants, New Mexico, 1979-2005. *Journal of radiological protection : official journal of the Society for Radiological Protection,* **28**(3), pp. 303-325.

BRENNER, D.J., 1994. The significance of dose rate in assessing the hazards of domestic radon exposure. *Health physics,* **67**(1), pp. 76-79.

BRENNER, D.J., DOLL, R., GOODHEAD, D.T., HALL, E.J., LAND, C.E., LITTLE, J.B., LUBIN, J.H., PRESTON, D.L., PRESTON, R.J., PUSKIN, J.S., RON, E., SACHS, R.K., SAMET, J.M., SETLOW, R.B. and ZAIDER, M., 2003. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proceedings of the National Academy of Sciences of the United States of America,* **100**(24), pp. 13761-13766.

BRENNER, D.J. and HALL, E.J., 1990. The inverse dose-rate effect for oncogenic transformation by neutrons and charged particles: a plausible interpretation consistent with published data. *International journal of radiation biology,* **58**(5), pp. 745-758.

BRENNER, D.J., HALL, E.J., RANDERS-PEHRSON, G. and MILLER, R.C., 1993. Mechanistic considerations on the dose-rate/LET dependence of oncogenic transformation by ionizing radiations. *Radiation research,* **133**(3), pp. 365-369.

BRENNER, D.J. and SACHS, R.K., 2003. Domestic radon risks may be dominated by bystander effects--but the risks are unlikely to be greater than we thought. *Health physics,* **85**(1), pp. 103-108.

BRESLOW, N.E. and DAY, N.E., 1987. *Statistical Methods in Cancer Research. Volume II—The Design and Analysis of Cohort Studies.* Publication 82. Lyon, France: International Agency for Research on Cancer (IARC).

BRESLOW, N.E. and DAY, N.E., 1980. *Statistical Methods in Cancer Research. Volume I - The Analysis of Case-Control*
Studies. Publication 32. Lyon, France: International Agency for Research on Cancer (IARC).

BROSS, I.D., 1967. Pertinency of an extraneous variable. *Journal of chronic diseases,* **20**(7), pp. 487-495.

BRUSKE-HOHLFELD, I., MOHNER, M., POHLABELN, H., AHRENS, W., BOLM-AUDORFF, U., KREIENBROCK, L., KREUZER, M., JAHN, I., WICHMANN, H.E. and JOCKEL, K.H., 2000. Occupational lung cancer risk for men in Germany: results from a pooled case-control study. *American Journal of Epidemiology,* **151**(4), pp. 384-395.

BRUSKE-HOHLFELD, I., ROSARIO, A.S., WOLKE, G., HEINRICH, J., KREUZER, M., KREIENBROCK, L. and WICHMANN, H.E., 2006. Lung cancer risk among former uranium miners of the WISMUT Company in Germany. *Health physics,* **90**(3), pp. 208-216.

BUCKLEY, J.P., KEIL, A.P., MCGRATH, L.J. and EDWARDS, J.K., 2015. Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology (Cambridge, Mass.),* **26**(2), pp. 204-212.

CANADIAN CANCER SOCIETY, 2016-last update, Smoking and Cancer [Homepage of Canadian Cancer Society], [Online]. Available: http://www.cancer.ca/en/prevention-and-screening/live-well/smoking-and-tobacco/smoking-and-cancer [12/10, 2016].

CANADIAN CANCER SOCIETY, 2013. *Canadian Cancer Statistics, 2013.* Toronto, ON: Canadian Cancer Society.

CHECKOWAY, H., PEARCE, N. and KRIEBEL, D., 2004. *Research Methods in Occupational Epidemiology. Monographs in Epidemiology and Biostatistics.* 34 edn. New York, NY: Oxford University Press.

CNSC, January 14, 2015, 2015-last update, Updated analysis of the Eldorado uranium miners' cohort: Part I of the Saskatchewan Uranium Miners' Cohort Study (RSP-0205) [Homepage of Canadian Nuclear Safety Commission], [Online]. Available: http://nuclearsafety.gc.ca/eng/resources/health/health-studies/eldorado/index.cfm [April 16, 2017].

CNSC, 02-03, 2014a-last update, Radon in Canada's Uranium Industry. Fact Sheet, March 2012 [Homepage of Canadian Nuclear Safety Commission], [Online]. Available: http://nuclearsafety.gc.ca/eng/resources/fact-sheets/radon-fact-sheet.cfm [12-31, 2015].

CNSC, 02-03, 2014b-last update, Uranium Mining and Milling: The Facts on a Well-Regulated Industry. Fact Sheet. July 2012 [Homepage of Canadian Nuclear Safety Commission], [Online]. Available: http://www.nuclearsafety.gc.ca/eng/resources/fact-sheets/uranium-mining-milling.cfm. [12-31, 2015].

CNSC, 2011a. *Introduction to Dosimetry.* INFO-0827. Ottawa, Ontario: Canadian Nuclear Safety Commission.

CNSC, 2011b. *Radon and Health.* INFO-0813. Ottawa, Ontario: Canadian Nuclear Safety Commission.

CNSC, 2006. *Updated analysis of the Eldorado uranium miners' cohort. Part I of the Saskatchewan Uranium Miners' Cohort Study.* RSP-0205. Ottawa, Ontario: Canadian Nuclear Safety Commission.

CNSC, 2004. *Summary report of the Eldorado nuclear cohort study: internal linkage, 'alive' follow-up, 1950-2000 mortality linkage, 1969-2000 cancer incidence linkage. (prepared by Statistics Canada).* RSP 0188. Ottawa, Ontaro: Canadian Nuclear Safety Commission.

CNSC, 2003. *Feasibility Study: Saskatchewan Uranium Miners Cohort Study, Part II* . RSP-0178. Ottawa, Ontario: Canadian Nuclear Safety Commission.

COLLIER, C.G., STRONG, J.C., HUMPHREYS, J.A., TIMPSON, N., BAKER, S.T., ELDRED, T., COBB, L., PAPWORTH, D. and HAYLOCK, R., 2005. Carcinogenicity of radon/radon decay product inhalation in rats--effect of dose, dose rate and unattached fraction. *International journal of radiation biology,* **81**(9), pp. 631-647.

CORNFIELD, J., HAENSZEL, W., HAMMOND, E.C., LILIENFELD, A.M., SHIMKIN, M.B. and WYNDER, E.L., 1959. Smoking and lung cancer: recent evidence and a discussion of some questions. *Journal of the National Cancer Institute,* **22**(1), pp. 173-203.

COSTELLO, S., FRIESEN, M.C., CHRISTIANI, D.C. and EISEN, E.A., 2011. Metalworking fluids and malignant melanoma in autoworkers. *Epidemiology (Cambridge, Mass.),* **22**(1), pp. 90-97.

DARBY, S., HILL, D., AUVINEN, A., BARROS-DIOS, J.M., BAYSSON, H., BOCHICCHIO, F., DEO, H., FALK, R., FORASTIERE, F., HAKAMA, M., HEID, I., KREIENBROCK, L., KREUZER, M., LAGARDE, F., MAKELAINEN, I., MUIRHEAD, C., OBERAIGNER, W., PERSHAGEN, G., RUANO-RAVINA, A., RUOSTEENOJA, E., ROSARIO, A.S., TIRMARCHE, M., TOMASEK, L., WHITLEY, E., WICHMANN, H.E. and DOLL, R., 2005. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ (Clinical research ed.),* **330**(7485), pp. 223.

DARBY, S., HILL, D., DEO, H., AUVINEN, A., BARROS-DIOS, J.M., BAYSSON, H., BOCHICCHIO, F., FALK, R., FARCHI, S., FIGUEIRAS, A., HAKAMA, M., HEID, I., HUNTER, N., KREIENBROCK, L., KREUZER, M., LAGARDE, F., MAKELAINEN, I., MUIRHEAD, C., OBERAIGNER, W., PERSHAGEN, G., RUOSTEENOJA, E., ROSARIO, A.S., TIRMARCHE, M., TOMASEK, L., WHITLEY, E., WICHMANN, H.E. and DOLL, R., 2006. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scandinavian journal of work, environment & health,* **32 Suppl 1**, pp. 1-83.

DARBY, S.C., RADFORD, E.P. and WHITLEY, E., 1995. Radon exposure and cancers other than lung cancer in Swedish iron miners. *Environmental health perspectives,* **103 Suppl 2**, pp. 45-47.

DARBY, S.C., WHITLEY, E., HOWE, G.R., HUTCHINGS, S.J., KUSIAK, R.A., LUBIN, J.H., MORRISON, H.I., TIRMARCHE, M., TOMASEK, L. and RADFORD, E.P., 1995. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *Journal of the National Cancer Institute,* **87**(5), pp. 378-384.

DORIA-ROSE, V.P. and MARCUS, P.M., 2009. Death certificates provide an adequate source of cause of death information when evaluating lung cancer mortality: an example from the Mayo Lung Project. *Lung Cancer,* **63**, pp. 295-300.

DRUBAY, D., ANCELET, S., ACKER, A., KREUZER, M., LAURIER, D. and RAGE, E., 2014. Kidney cancer mortality and ionizing radiation among French and German uranium miners. *Radiation and environmental biophysics,* **53**(3), pp. 505-513.

DRUBAY, D., CAER-LORHO, S., LAROCHE, P., ACKER, A., LAURIER, D. and RAGE, E., 2014. Circulatory system disease mortality among French uranium miners. *Occupational and environmental medicine,* **71 Suppl 1**, pp. A24-5.

DUFEY, F., WALSH, L., SOGL, M., TSCHENSE, A., SCHNELZER, M. and KREUZER, M., 2013. Radiation dose dependent risk of liver cancer mortality in the German uranium miners' cohort 1946-2003. *Journal of radiological protection : official journal of the Society for Radiological Protection,* **33**(1), pp. 175-185.

DUPORT, P., 2002. Is the radon risk overestimated? Neglected doses in the estimation of the risk of lung cancer in uranium underground miners. *Radiation Protection Dosimetry,* **98**(3), pp. 329-338.

EDWARDS, J.K., MCGRATH, L.J., BUCKLEY, J.P., SCHUBAUER-BERIGAN, M.K., COLE, S.R. and RICHARDSON, D.B., 2014. Occupational radon exposure and lung cancer mortality: estimating intervention effects using the parametric g-formula. *Epidemiology (Cambridge, Mass.),* **25**(6), pp. 829-834.

GANDINI, S., BOTTERI, E., IODICE, S., BONIO, M., LOWENFELS, A.B., MAISONNEUVE, P. and BOYLE, P., 2008. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer,* **122**(1), pp. 155-164.

GARSHICK, E., LADEN, F., HART, J.E., DAVIS, M.E., EISEN, E.A. and SMITH, T.J., 2012. Lung cancer and elemental carbon exposure in trucking industry workers. *Environmental health perspectives,* **120**(9), pp. 1301-1306.

GILBERT, E.S., 1982. Some confounding factors in the study of mortality and occupational exposures. *American Journal of Epidemiology,* **116**(1), pp. 177-188.

GOLDBERG, M.,S., CARPENTER, M., THERIAULT, G. and FAIR, M., 1993. The accuracy of ascertaining vital status in a historical cohort study of synthetic textiles workers using computerized record linkage to the Canadian Mortality Data Base. *Canadian Journal of Public Health,* **84**, pp. 201-204.

GOLDSMITH, J.R., 1975. Letter: What do we expect from an occupational cohort? *Journal of occupational medicine.: official publication of the Industrial Medical Association,* **17**(2), pp. 126-131.

GREENLAND, S., PEARL, J. and ROBINS, J.M., 1999. Causal diagrams for epidemiologic research. *Epidemiology,* **10**, pp. 37-48.

GROSCHE, B., KREUZER, M., KREISHEIMER, M., SCHNELZER, M. and TSCHENSE, A., 2006. Lung cancer risk among German male uranium miners: a cohort study, 1946-1998. *British journal of cancer,* **95**(9), pp. 1280-1287.

HARLEY, J.H., 1980. Sampling and measurement of airborne daughter products of radon. (Reprinted). *Health Phys,* **38**, pp. 106.

HARLEY, J.H., 1953. Sampling and measurement of airborne daughter products of radon. *Nucleonics,* **11**, pp. 12-15.

HARLEY, J.H., 1952. *Sampling and measurement of airborne daughter products of radon. Doctoral dissertation.*, Rensselaer Polytechnic Institute.

HARLEY, J.H., 1981. Radioactive emissions and radon. *Bull N Y Acad Med,* **57**(10), pp. 883-96-896.

HARTING, F.H. and HESSE, W., 1879. Der Lungerkrebs, die Bergkrankheit in den Schneeberger Gruben. *Viertel Gerichtl Med Oeff Sanitaetswes,* **31**, pp. 102-132; 313-337.

HEALTH CANADA, 2016. *Radon Progeny (WLM) for Uranium Miners 2005-2015.* Data extracted and produced edn. Ottawa, Ontario: Minister of Health.

HEALTH CANADA, 2012. *Cross-Canada Survey on Radon Concentrations in Homes. Final Report.* H144-2/2012E. Ottawa, Ontario: Minister of Health.

HEALTH CANADA, 2008. *2007 Report on Occupational Radiation Exposures in Canada.* HC Pub: 5904. Ottawa, Canada: Ministry of Health.

HEALTH CANADA, 2001. *2001 Report on Occupational Radiation Exposures in Canada.* H46-2/01-258E. Ottawa, Ontario: Minster of Health.

HEI DIESEL EPIDEMIOLOGY PANEL, 2015. *Executive Summary. Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment.* HEI Special Report 19. Bost, MA: Health Effects Institute.

HODGSON, J.T. and JONES, R.D., 1990. Mortality of a cohort of tin miners 1941-86. [published erratum appears in Br J Ind Med 47;846,1990]. *Br J Ind Med,* **47**, pp. 665-676.

HOOVER, H.C. and HOOVER, L.H., 1950. *Georgius Agricola De Re Metalallica.* New York, U.S.A.: Dover Publications.

HORNUNG, R.W., DEDDENS, J. and ROSCOE, R., 1995. Modifiers of exposure-response estimates for lung cancer among miners exposed to radon progeny. *Environmental health perspectives,* **103 Suppl 2**, pp. 49-53.

HORNUNG, R.W. and MEINHARDT, T.J., 1987. Quantitative risk assessment of lung cancer in U.S. uranium miners. *Health physics,* **52**(4), pp. 417-430.

HOWE, G.R., 1998. Use of computerized record linkage in cohort studies. *Epidemiologic reviews,* **20**(1), pp. 112-121.

HOWE, G.R., NAIR, R.C., NEWCOMBE, H.B., MILLER, A.B. and ABBATT, J.D., 1986. Lung cancer mortality (1950-80) in relation to radon daughter exposure in a cohort of workers at the Eldorado Beaverlodge uranium mine. *Journal of the National Cancer Institute,* **77**(2), pp. 357-362.

HOWE, G.R., NAIR, R.C., NEWCOMBE, H.B., MILLER, A.B., BURCH, J.D. and ABBATT, J.D., 1987. Lung cancer mortality (1950-80) in relation to radon daughter exposure in a cohort of workers at the Eldorado Port Radium uranium mine: possible modification of risk by exposure rate. *Journal of the National Cancer Institute,* **79**(6), pp. 1255-1260.

HUNTER, N., MUIRHEAD, C.R., BOCHICCHIO, F. and HAYLOCK, R.G., 2015. Calculation of lifetime lung cancer risks associated with radon exposure, based on various models and exposure scenarios. *Journal of radiological protection : official journal of the Society for Radiological Protection,* **35**(3), pp. 539-555.

HUNTER, N., MUIRHEAD, C.R., TOMÁŠEK, L., KREUZER, M., LAURIER, D., LEURAUD, K., SCHNELZER, M., GROSCHE, B., PLACEK, V., HERIBANOVA, A. and TIRMARCHE, M., 2013. Joint Analysis of Three European Nested Case-control Studies of Lung Cancer among Radon Exposed Miners: Exposure Restricted to Below 300 WLM. *Health physics,* **104**(3), pp. 282-292.

IAEA, 2015. *Protection of the Public against Exposure Indoors due to Radon and Other Natural Sources of Radiation.* No. SSG-32 STI/PUB/1651 edn. Vienna, Austria: International Atomic Energy Agency.

IAEA, 2014. *Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards: General Safety Requirements Part 3.* No. GSR Part 3 STI/PUB/1578 edn. Vienna, Austria: International Atomic Energy Agency.

IARC, 2013. *Diesel and Gasoline Engine Exhausts and Some Nitroarenes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer.* 105 edn. Lyon, France: World Health Organization.

IARC, 2012a. *Arsenic, Metals, Fibres and Dusts. A Review of Human Carcinogens. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer.* 100C edn. Lyon, France: World Health Organization.

IARC, 2012b. *Personal Habits and Indoor Combustions. A Review of Human Carcinogens. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer.* 100E edn. Lyon, France: World Health Organization.

IARC, 2012c. *Radiation. A Review of Human Carcinogens. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer.* 100D edn. Lyon, France: World Health Organization.

IARC, 2001. *Ionizing Radiation, Part 2: Some Internally Deposited Radionuclides. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer.* 78 edn. Lyon, France: World Health Organization.

IARC, 1988. *Man-made Mineral Fibres and Radon. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer.* 43 edn. Lyon, France: World Health Organization.

IARC, 1986. *Tobacco Smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer.* 38 edn. Lyon, France: World Health Organization.

ICRP, 2010. *Lung cancer risk from radon and progeny and statement on radon.* ICRP Publication 115 edn. Oxford, England: Pergamon Press.

ICRP, 2007a. *The 2007 Recommendations of the International Commission on Radiological Protection.* ICRP Publication 103 edn. Oxford, England: Pergamon Press.

ICRP, 2007b. *Extract: The 2007 Recommendations of the International Commission on Radiological Protection* . ICRP Publication 103 edn. Oxford, England: Pergamon Press.

ICRP, 1993. *Protection Against Radon-222 at Home and at Work.* Publication 65 edn. Oxford, England: Pergamon Press.

IRSN, 2013. *The Effects of Radiation on our Health.* Paris, France: Institut de Radioprotection et de Surete Nucléaire.

JACOBI, W., 1994. *The History of the Radon Problem in Mines and Homes. Protection Against Radon- 222 at Home and at Work.* London, England: Pergamon Press.

JONSSON, H., BERGDAHL, I.A., AKERBLOM, G., ERIKSSON, K., ANDERSSON, K., KAGSTROM, L., JARVHOLM, B. and DAMBER, L., 2010. Lung cancer risk and radon exposure in a cohort of iron ore miners in Malmberget, Sweden. *Occupational and environmental medicine,* **67**(8), pp. 519-525.

KADHIM, M., SALOMAA, S., WRIGHT, E., HILDEBRANDT, G., BELYAKOV, O.V., PRISE, K.M. and LITTLE, M.P., 2013. Non-targeted effects of ionising radiation--implications for low dose risk. *Mutation research,* **752**(2), pp. 84-98.

KEIL, A.P., RICHARDSON, D.B. and TROESTER, M.A., 2015. Healthy worker survivor bias in the Colorado Plateau uranium miners cohort. *American Journal of Epidemiology,* **181**(10), pp. 762-770.

KELLERER, A.M. and ROSSI, H.H., 2012. A generalized formulation of dual radiation action. *Radiation research,* **178**(2), pp. AV204-13.

KREUZER, M., BRACHNER, A., LEHMANN, F., MARTIGNONI, K., WICHMANN, H.E. and GROSCHE, B., 2002. Characteristics of the German uranium miners cohort study. *Health physics,* **83**(1), pp. 26-34.

KREUZER, M., DUFEY, F., LAURIER, D., NOWAK, D., MARSH, J.W., SCHNELZER, M., SOGL, M. and WALSH, L., 2015. Mortality from internal and external radiation exposure in a cohort of male German uranium millers, 1946-2008. *International archives of occupational and environmental health,* **88**(4), pp. 431-441.

KREUZER, M., DUFEY, F., SOGL, M., SCHNELZER, M. and WALSH, L., 2013. External gamma radiation and mortality from cardiovascular diseases in the German WISMUT uranium miners cohort study, 1946-2008. *Radiation and environmental biophysics,* **52**(1), pp. 37-46.

KREUZER, M., FENSKE, N., SCHNELZER, M. and WALSH, L., 2015. Lung cancer risk at low radon exposure rates in German uranium miners. *British journal of cancer,* **113**(9), pp. 1367-1369.

KREUZER, M., GROSCHE, B., BRACHNER, A., MARTIGNONI, K., SCHNELZER, M., SCHOPKA, H.J., BRUSKE-HOHLFELD, I., WICHMANN, H.E. and BURKART, W., 1999. The German uranium miners cohort study: feasibility and first results. *Radiation research,* **152**(6 Suppl), pp. S56-8.

KREUZER, M., GROSCHE, B., SCHNELZER, M., TSCHENSE, A., DUFEY, F. and WALSH, L., 2010. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946-2003. *Radiation and environmental biophysics,* **49**(2), pp. 177-185.

KREUZER, M., KREISHEIMER, M., KANDEL, M., SCHNELZER, M., TSCHENSE, A. and GROSCHE, B., 2006. Mortality from cardiovascular diseases in the German uranium miners cohort study, 1946-1998. *Radiation and environmental biophysics,* **45**(3), pp. 159-166.

KREUZER, M., SCHNELZER, M., TSCHENSE, A., WALSH, L. and GROSCHE, B., 2010. Cohort profile: the German uranium miners cohort study (WISMUT cohort), 1946-2003. *International journal of epidemiology,* **39**(4), pp. 980-987.

KREUZER, M., SOBOTZKI, C., FENSKE, N., MARSH, J.W. and SCHNELZER, M., 2017. Leukaemia mortality and low-dose ionising radiation in the WISMUT uranium miner cohort (1946-2013). *Occupational and environmental medicine,* **74**(4), pp. 252-258.

KREUZER, M., STRAIF, K., MARSH, J.W., DUFEY, F., GROSCHE, B., NOSSKE, D. and SOGL, M., 2012. Occupational dust and radiation exposure and mortality from stomach cancer among German uranium miners, 1946-2003. *Occupational and environmental medicine,* **69**(3), pp. 217-223.

KREUZER, M., WALSH, L., SCHNELZER, M., TSCHENSE, A. and GROSCHE, B., 2008. Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960-2003. *British journal of cancer,* **99**(11), pp. 1946-1953.

KREWSKI, D., LUBIN, J.H., ZIELINSKI, J.M., ALAVANJA, M., CATALAN, V.S., FIELD, R.W., KLOTZ, J.B., LETOURNEAU, E.G., LYNCH, C.F., LYON, J.I., SANDLER, D.P., SCHOENBERG, J.B., STECK, D.J., STOLWIJK, J.A., WEINBERG, C. and WILCOX, H.B., 2005. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology (Cambridge, Mass.),* **16**(2), pp. 137-145.

KREWSKI, D., LUBIN, J.H., ZIELINSKI, J.M., ALAVANJA, M., CATALAN, V.S., FIELD, R.W., KLOTZ, J.B., LETOURNEAU, E.G., LYNCH, C.F., LYON, J.L., SANDLER, D.P., SCHOENBERG, J.B., STECK, D.J., STOLWIJK, J.A., WEINBERG, C. and WILCOX, H.B., 2006. A combined analysis of North American case-control studies of residential radon and lung cancer. *Journal of toxicology and environmental health. Part A,* **69**(7), pp. 533-597.

KULICH, M., RERICHA, V., RERICHA, R., SHORE, D.L. and SANDLER, D.P., 2011. Incidence of non-lung solid cancers in Czech uranium miners: a case-cohort study. *Environmental research,* **111**(3), pp. 400-405.

KUNZ, E., SEVC, J. and PLACEK, V., 1978. Lung cancer mortality in uranium miners (methodological aspects). *Health physics,* **35**(4), pp. 579-580.

KUNZ, E., SEVC, J., PLACEK, V. and HORACEK, J., 1979. Lung cancer in man in relation to different time distribution of radiation exposure. *Health physics,* **36**(6), pp. 699-706.

KUSIAK, R.A., RITCHIE, A.C., MULLER, J. and SPRINGER, J., 1993. Mortality from lung cancer in Ontario uranium miners. *British journal of industrial medicine,* **50**(10), pp. 920-928.

L'ABBÉ, K.A., HOWE, G.R., BURCH, J.D., MILLER, A.B., ABBATT, J., BAND, P., CHOI, W., DU, J., FEATHER, J. and GALLAGHER, R., 1991. Radon exposure, cigarette smoking, and other mining experience in the Beaverlodge uranium miners cohort. *Health physics,* **60**(4), pp. 489-495.

LANE, R.S., FROST, S.E., HOWE, G.R. and ZABLOTSKA, L.B., 2010. Mortality (1950-1999) and cancer incidence (1969-1999) in the cohort of Eldorado uranium workers. *Radiation research,* **174**(6), pp. 773-785.

LANGARD, S., 2015. Gregorius Agricola memorial lecture: Lung cancer-A work-related disease for 500 years, as predicted by Agricola. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS),* **31**, pp. 214-218.

LAST, J.A., 1995. *Dictionary of Epidemiology.* 3 edn. Oxford, UK: Oxford University Press.

LAURIER, D., TIRMARCHE, M., MITTON, N., VALENTY, M., RICHARD, P., POVEDA, S., GELAS, J.M. and QUESNE, B., 2004. An update of cancer mortality among the French cohort of uranium miners: extended follow-up and new source of data for causes of death. *European journal of epidemiology,* **19**(2), pp. 139-146.

LETOURNEAU, E.G., KREWSKI, D., CHOI, N.W., GODDARD, M.J., MCGREGOR, R.G., ZIELINSKI, J.M. and DU, J., 1994. Case-control study of residential radon and lung cancer in Winnipeg, Manitoba, Canada. *American Journal of Epidemiology,* **140**(4), pp. 310-322.

LEURAUD, K., BILLON, S., BERGOT, D., TIRMARCHE, M., CAER, S., QUESNE, B. and LAURIER, D., 2007. Lung cancer risk associated to exposure to radon and smoking in a case-control study of French uranium miners. *Health physics,* **92**(4), pp. 371-378.

LEURAUD, K., SCHNELZER, M., TOMÁŠEK, L., HUNTER, N., TIRMARCHE, M., GROSCHE, B., KREUZER, M. and LAURIER, D., 2011. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. *Radiation research,* **176**(3), pp. 375-387.

LEVIN, L.I., ZHENG, W., BLOT, W.J., GAO, Y.T. and FRAUMENI, J.F., Jr, 1988. Occupation and lung cancer in Shanghai: a case-control study. *British journal of industrial medicine,* **45**(7), pp. 450-458.

LITTLE, M.P., 2010. Do non-targeted effects increase or decrease low dose risk in relation to the linear-non-threshold (LNT) model? *Mutation research,* **687**(1-2), pp. 17-27.

LITTLE, M.P., 2004. The bystander effect model of Brenner and Sachs fitted to lung cancer data in 11 cohorts of underground miners, and equivalence of fit of a linear relative risk model with adjustment for attained age and age at exposure. *Journal of radiological protection : official journal of the Society for Radiological Protection,* **24**(3), pp. 243-255.

LITTLE, M.P. and WAKEFORD, R., 2002. The bystander effect in experimental systems and compatibility with radon-induced lung cancer in humans. *Journal of radiological protection : official journal of the Society for Radiological Protection,* **22**(3A), pp. A27-31.

LOOMIS, D., RICHARDSON, D.B. and ELLIOTT, L., 2005. Poisson regression analysis of ungrouped data. *Occupational and environmental medicine,* **62**(5), pp. 325-329.

LORENZ, E., 1944. Radioactivity and lung cancer: A critical review of lung cancer in the miners of Schneeberg and Joachimsthal. *J Natl Cancer Inst,* **5**, pp. 1-15.

LUBIN, J.H., BOICE, J.D., EDLING, C., HORNUNG, R.W., HOWE, G., KUNZ, E., KUSIAK, R.A., MORRISON, H.I., RADFORD, E.P. and PIERCE, D.A., 1994. *Radon and lung cancer risk: A joint analysis of 11 underground miners studies.* 94-3644. Bethesda, MD.: National Institutes of Health.

LUBIN, J.H. and BOICE, J.D.,Jr, 1997. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. *Journal of the National Cancer Institute,* **89**(1), pp. 49-57.

LUBIN, J.H., BOICE, J.D.,Jr, EDLING, C., HORNUNG, R.W., HOWE, G., KUNZ, E., KUSIAK, R.A., MORRISON, H.I., RADFORD, E.P. and SAMET, J.M., 1995a. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health physics,* **69**(4), pp. 494-500.

LUBIN, J.H., BOICE, J.D.,Jr, EDLING, C., HORNUNG, R.W., HOWE, G.R., KUNZ, E., KUSIAK, R.A., MORRISON, H.I., RADFORD, E.P. and SAMET, J.M., 1995b. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *Journal of the National Cancer Institute,* **87**(11), pp. 817-827.

LUBIN, J.H., LIANG, Z., HRUBEC, Z., PERSHAGEN, G., SCHOENBERG, J.B., BLOT, W.J., KLOTZ, J.B., XU, Z.Y. and BOICE, J.D.,Jr, 1994. Radon exposure in residences and lung cancer among women: combined analysis of three studies. *Cancer causes & control : CCC,* **5**(2), pp. 114-128.

LUBIN, J.H., POTTERN, L.M., STONE, B.J. and FRAUMENI, J.F., Jr, 2000. Respiratory cancer in a cohort of copper smelter workers: results from more than 50 years of follow-up. *American Journal of Epidemiology,* **151**(6), pp. 554-565.

LUBIN, J.H., TOMASEK, L., EDLING, C., HORNUNG, R.W., HOWE, G., KUNZ, E., KUSIAK, R.A., MORRISON, H.I., RADFORD, E.P., SAMET, J.M., TIRMARCHE, M., WOODWARD, A. and YAO, S.X., 1997. Estimating lung cancer mortality from residential radon using data for low exposures of miners. *Radiation research,* **147**(2), pp. 126-134.

LUBIN, J.H., WANG, Z.Y., BOICE, J.D.,Jr, XU, Z.Y., BLOT, W.J., DE WANG, L. and KLEINERMAN, R.A., 2004. Risk of lung cancer and residential radon in China: pooled results of two studies. *International journal of cancer. Journal international du cancer,* **109**(1), pp. 132-137.

LUDWIG, P. and LORENSER, S., 1924. Untersuchungen der grubenluft in den Schneeberger gruben auf den gehalt an radiumemanation. *Z Physik,* **22**, pp. 178-185.

MARSH, J.W., BLANCHARDON, E., GREGORATTO, D., HOFMANN, W., KARCHER, K., NOSSKE, D. and TOMÁŠEK, L., 2012. Dosimetric calculations for uranium miners for epidemiological studies. *Radiation Protection Dosimetry,* **149**(4), pp. 371-383.

MARSH, J.W., HARRISON, J.D., LAURIER, D., BIRCHALL, A., BLANCHARDON, E., PAQUET, F. and TIRMARCHE, M., 2014. Doses and lung cancer risks from exposure to radon and plutonium. *International journal of radiation biology,* , pp. 1-19.

MARUSIAKOVA, M., GREGOR, Z. and TOMÁŠEK, L., 2011. A review of exposures to radon, long-lived radionuclides and external gamma at the Czech uranium mine. *Radiation Protection Dosimetry,* **145**(2-3), pp. 248-251.

MCMICHAEL, A.J., 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. *Journal of occupational medicine.: official publication of the Industrial Medical Association,* **18**(3), pp. 165-168.

MCMICHAEL, A.J., SPIRTAS, R. and KUPPER, L.L., 1974. An epidemiologic study of mortality within a cohort of rubber workers, 1964-72. *Journal of occupational medicine.: official publication of the Industrial Medical Association,* **16**(7), pp. 458-464.

MILLER, R.C., RANDERS-PEHRSON, G., HIEBER, L., MARINO, S.A., RICHARDS, M. and HALL, E.J., 1993. The inverse dose-rate effect for oncogenic transformation by charged particles is dependent on linear energy transfer. *Radiation research,* **133**(3), pp. 360-364.

MINISTER OF JUSTICE, 2000. *Radiation Protection Regulations (SOR/2000-203).* Regulations edn. Canada: Canada.

MINISTER OF JUSTICE, 1997. *Nuclear Safety and Control Act (S.C. 1997, c.9).* Act edn. Canada: Canada.

MORLIER, J.P., MORIN, M., CHAMEAUD, J., MASSE, R., BOTTARD, S. and LAFUMA, J., 1992. Importance of the role of dose rate on tumor induction in rats after radon inhalation. *Comptes rendus de l'Academie des sciences. Serie III, Sciences de la vie,* **315**(12), pp. 463-466.

MORRISON, H.I., SEMENCIW, R.M., MAO, Y. and WIGLE, D.T., 1988. Cancer mortality among a group of fluorspar miners exposed to radon progeny. *American Journal of Epidemiology,* **128**(6), pp. 1266-1275.

NATIONAL RESEARCH COUNCIL, 2006. *Health Risks from Exposure to Low Levels of Ionizing Radiation, Phase 2. BEIR VII Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation.* Washington, D.C.: The National Academies Press.

NATIONAL RESEARCH COUNCIL, 1999. *Health Effects of Exposure to Radon. BEIR VI Committee on Health Risks of Exposure to Radon. Board on Radiation Effects Research Commission on Life Sciences.* Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL, 1991. *Panel on Dosimetric Assumptions Affecting the Application of Radon Risk Estimates. Comparative Dosimetry of Radon in Mines and Homes.* Washington, D.C.: National Academy Press.

NATIONAL RESEARCH COUNCIL, 1988. *Health risks of radon and other internally deposited alpha-emitters: BEIR IV Committee on the Biological Effects of Ionizing Radiations.* Washington, D.C.: National Academy Press.

NAVARANJAN, G., BERRIAULT, C., DO, M., VILLENEUVE, P.J. and DEMERS, P.A., 2016. Cancer incidence and mortality from exposure to radon progeny among Ontario uranium miners. *Occupational and environmental medicine,* **73**(12), pp. 838-845.

NEA-OECD, 2014. *Uranium 2014: Resources, Production and Demand. A Joint Report by the OECD Nuclear Energy Agency and the International Atomic Energy Agency.* NEA No. 7210. Nuclear Energy Agency - Organisation for Economic Co-operation and Development.

NUSINOVICI, S., VACQUIER, B., LEURAUD, K., METZ-FLAMANT, C., CAER-LORHO, S., ACKER, A. and LAURIER, D., 2010. Mortality from circulatory system diseases and low-level radon exposure in the French cohort study of uranium miners, 1946-1999. *Scandinavian journal of work, environment & health,* **36**(5), pp. 373-383.

OFFICE OF THE PRIVACY COMMISSIONER OF CANADA, February 17, 2014-last update, Fact Sheets: Social Insurance Number (SIN). Available: www.priv.gc.ca/resource/fs-fi/02_05_502_e.asp [June 3, 2016].

OGLE, W., 1885. *Letter to the Registrar General on the mortality in the registration districts of England and Wales during the ten years 1871-1880. Supplement to the 45th Annual Report of the Registrar General of Births, Deaths and Marriages in England.* London: Registrar General.

OTAHAL, P., BURIAN, I., NASIR, M.M. and GREGOR, Z., 2014. Radon contribution to the total effective dose of uranium miners. *Radiation Protection Dosimetry,* **160**(1-3), pp. 117-119.

PEARL, J., 1995. Causal diagrams for empirical research. *Biometrika,* **82**, pp. 669-688.

PERSHAGEN, G., AKERBLOM, G., AXELSON, O., CLAVENSJO, B., DAMBER, L., DESAI, G., ENFLO, A., LAGARDE, F., MELLANDER, H. and SVARTENGREN, M., 1994. Residential radon exposure and lung cancer in Sweden. *The New England journal of medicine,* **330**(3), pp. 159-164.

PERSHAGEN, G., LIANG, Z.H., HRUBEC, Z., SVENSSON, C. and BOICE, J.D.,Jr, 1992. Residential radon exposure and lung cancer in Swedish women. *Health physics,* **63**(2), pp. 179-186.

PICCIOTTO, S. and HERTZ-PICCIOTTO, I., 2015. Commentary: healthy worker survivor bias: a still-evolving concept. *Epidemiology (Cambridge, Mass.),* **26**(2), pp. 213-215.

PIRCHAN, A. and SIKL, H., 1932. Cancer of the lung in the miners of Jachymov. *Am J Cancer,* **16**, pp. 681-722.

PLACEK, V., TOMASEK, L., KUNZ, E. and HERIBANOVA, A., 1997. Lung cancer and exposure to radon under present mining conditions. *Pracov. Lek. [in Czech],* **49**, pp. 14-20.

PRESTON DL, LUBIN JH, PIERCE DA, MCCONNEY ME, SHILNIKOVA NS., 2002. *EPIWIN: EPICURE for Windows (Last updated 13/05/2002).* 1.1.0.0 edn. HiroSoft International Corporation and Risk Sciences International.

PRESTON, D.L., LUBIN, J.H., PIERCE, D.A. and ET AL., 1993. *EPICURE User's Guide.* Seattle,W.A.: Hirosoft International Corporation.

PRESTON, D.L., LUBIN, J.H., PIERCE, D.A., MCCONNEY, M.E. and SHILNIKOVA, N.S., 2015. *EPICURE Version 2 User Guide. 1988 -2015.* Seattle: HiroSoft International Corporation and Risk Sciences International.

PRESTON, D., 1996. Statistical Methods in Studies of Radiation Risk. *SAS Conference Proceedings South East SAS Users Group (SESUG) 1996 Proceedings.,* October 13-15, 1996 1996, Lex Jansen and SAS Institute Inc., pp. 436-442.

PRESTON, D.L., SHIMIZU, Y., PIERCE, D.A., SUYAMA, A. and MABUCHI, K., 2003. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiation research,* **160**(4), pp. 381-407.

PROCTOR, R.N., 1995. *Cancer Wars. How Politics Shapes What We Know and Don't Know About Cancer.* New York, U.S.A.: Basic Books.

PUSKIN, J.S., 2003. Smoking as a confounder in ecologic correlations of cancer mortality rates with average county radon levels. *Health physics,* **84**(4), pp. 526-532.

RADFORD, E.P. and RENARD, K.G., 1984. Lung cancer in Swedish iron miners exposed to low doses of radon daughters. *The New England journal of medicine,* **310**(23), pp. 1485-1494.

RAGE, E., CAER-LORHO, S., DRUBAY, D., ANCELET, S., LAROCHE, P. and LAURIER, D., 2015. Mortality analyses in the updated French cohort of uranium miners (1946-2007). *International archives of occupational and environmental health,* **88**(6), pp. 717-730.

RAGE, E., CAER-LORHO, S., DRUBAY, D., ANCELET, S., LAROCHE, P. and LAURIER, D., 2014. Mortality analyses in the updated French cohort of uranium miners (1946-2007). *International archives of occupational and environmental health.,* **88**(6), pp. 717-730.

RAGE, E., VACQUIER, B., BLANCHARDON, E., ALLODJI, R.S., MARSH, J.W., CAER-LORHO, S., ACKER, A. and LAURIER, D., 2012. Risk of lung cancer mortality in relation to lung doses among French uranium miners: follow-up 1956-1999. *Radiation research,* **177**(3), pp. 288-297.

RERICHA, V., KULICH, M., RERICHA, R., SHORE, D.L. and SANDLER, D.P., 2006. Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. *Environmental health perspectives,* **114**(6), pp. 818-822.

RICHARDSON, D.B. and LANGHOLZ, B., 2012. Background stratified Poisson regression analysis of cohort data. *Radiation and environmental biophysics,* **51**(1), pp. 15-22.

RICHARDSON, D.B., LAURIER, D., SCHUBAUER-BERIGAN, M.K., TCHETGEN TCHETGEN, E. and COLE, S.R., 2014. Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. *American Journal of Epidemiology,* **180**(9), pp. 933-940.

RICHARDSON, D.B. and LOOMIS, D., 2004. The impact of exposure categorisation for grouped analyses of cohort data. *Occupational and environmental medicine,* **61**(11), pp. 930-935.

RICHIARDI, L., FORASTIERE, F., BOFFETTA, P., SIMONATO, L. and MERLETTI, F., 2005. Effect of different approaches to treatment of smoking as a potential confounder in a case-control study on occupational exposures. *Occupational and environmental medicine,* **62**(2), pp. 101-104.

ROBINS, J., 1986. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. *Math Model,* **7**(9-12), pp. 1393-1512.

ROTHMAN, K.J., ed, 2002. *Epidemiology. An Introduction.* Oxford: Oxford University Press.

ROTHMAN, K.J., GREENLAND, S. and LASH, T.L., 2008. *Modern Epidemiology.* Third edn. Philadelphia, PA, USA: Lippincott Williams & Wilkins.

SABOL, J., JURDA, M., GREGOR, Z. and NAVRATIL, L., 2011. Assessment of the total effective dose of miners in the underground Rozna Uranium Mine in the Czech Republic during the period 2004-2009. *Radiation Protection Dosimetry,* **144**(1-4), pp. 615-619.

SAMET, J.M., 2011. Radiation and cancer risk: a continuing challenge for epidemiologists. *Environmental health : a global access science source,* **10 Suppl 1**, pp. S4-069X-10-S1-S4.

SAMET, J.M., PATHAK, D.R., MORGAN, M.V., KEY, C.R., VALDIVIA, A.A. and LUBIN, J.H., 1991. Lung cancer mortality and exposure to radon progeny in a cohort of New Mexico underground uranium miners. *Health physics,* **61**(6), pp. 745-752.

SCHNELZER, M., HAMMER, G.P., KREUZER, M., TSCHENSE, A. and GROSCHE, B., 2010. Accounting for smoking in the radon-related lung cancer risk among German uranium miners: results of a nested case-control study. *Health physics,* **98**(1), pp. 20-28.

SCHOENBERG, J.B., KLOTZ, J.B., WILCOX, H.B., NICHOLLS, G.P., GIL-DEL-REAL, M.T., STEMHAGEN, A. and MASON, T.J., 1990. Case-control study of residential radon and lung cancer among New Jersey women. *Cancer research,* **50**(20), pp. 6520-6524.

SCHUBAUER-BERIGAN, M.K., DANIELS, R.D. and PINKERTON, L.E., 2009. Radon exposure and mortality among white and American Indian uranium miners: an update of the Colorado Plateau cohort. *American Journal of Epidemiology,* **169**(6), pp. 718-730.

SCHUBAUER-BERIGAN, M.K. and WENZL, T.B., 2001. Leukemia mortality among radiation-exposed workers. *Occupational medicine (Philadelphia, Pa.),* **16**(2), pp. 271-287.

SENES CONSULTANTS LIMITED, 1996.
An algorithm for estimating radon decay product exposures from underground employment at the Eldorado Beaverlodge Mine. Ottawa, Ontario: Atomic Energy Control Board of Canada.

SEVC, J. and CECH, J., 1966. Concentration of Rn-222 and its decay products in some Czechoslovak mines. *Pracov. Lek. [in Czech],* **18**, pp. 438-442.

SEVC, J., KUNZ, E. and PLACEK, V., 1976. Lung cancer in uranium miners and long-term exposure to radon daughter products. *Health physics,* **30**(6), pp. 433-437.

SEVC, J., KUNZ, E., TOMASEK, L., PLACEK, V. and HORACEK, J., 1988. Cancer in man after exposure to Rn daughters. *Health physics,* **54**(1), pp. 27-46.

SEVC, J., TOMASEK, L., KUNZ, E., PLACEK, V., CHMELEVSKY, D., BARCLAY, D. and KELLERER, A.M., 1993. A survey of the Czechoslovak follow-up of lung cancer mortality in uranium miners. *Health physics,* **64**(4), pp. 355-369.

SHAH, D., 2009. Healthy worker effect phenomenon. *Indian journal of occupational and environmental medicine,* **13**(2), pp. 77-79.

SHIN, H.H., CAKMAK, S., BRION, O., VILLENEUVE, P., TURNER, M.C., GOLDBERG, M.S., JERRETT, M., CHEN, H., CROUSE, D., PETERS, P., POPE, C.A.,3rd and BURNETT, R.T., 2014. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. *Environmental research,* .

SIEMIATYCKI, J., WACHOLDER, S., DEWAR, R., WALD, L., BEGIN, D., RICHARDSON, L., ROSENMAN, K. and GERIN, M., 1988. Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? *American Journal of Industrial Medicine,* **13**(1), pp. 59-69.

SILVERMAN, D.T., SAMANIC, C.M., LUBIN, J.H., BLAIR, A.E., STEWART, P.A., VERMEULEN, R., COBLE, J.B., ROTHMAN, N., SCHLEIFF, P.L., TRAVIS, W.D., ZIEGLER, R.G., WACHOLDER, S. and ATTFIELD, M.D., 2012. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. *Journal of the National Cancer Institute,* **104**(11), pp. 855-868.

STATISTICS CANADA, 2014-09-09, 2014-last update, Record Linkage Program [Homepage of Statistics Canada], [Online]. Available: http://www.statcan.gc.ca/eng/health/link [11/19, 2016].

STATISTICS CANADA, 2013. An examination of the NAACCR method of assessing completeness of case ascertainment using the Canadian Cancer Registry (by D Zakaria). *Health Reports, Catalogue no. 82-003-X,* **24**(8), pp. 3-13.

STAYNER, L., STEENLAND, K., DOSEMECI, M. and HERTZ-PICCIOTTO, I., 2003. Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scandinavian journal of work, environment & health,* **29**(4), pp. 317-324.

STEENLAND, K., DEDDENS, J., SALVAN, A. and STAYNER, L., 1996. Negative bias in exposure response trends in occupational studies: modeling the healthy workers survivor effect. *Am J Epidemiol,* **143**, pp. 202-210.

STEENLAND, K. and STAYNER, L., 1991. The importance of employment status in occupational cohort mortality studies. *Epidemiology,* **2**, pp. 418-423.

SUISSA, S., 2008. Immortal time bias in pharmaco-epidemiology. *American Journal of Epidemiology,* **167**(4), pp. 492-499.

THOMAS, D.C., 2014. Invited commentary: is it time to retire the "pack-years" variable? Maybe not! *American Journal of Epidemiology,* **179**(3), pp. 299-302.

THOMPKINS, R.W., 1982. Radiation in uranium mines: A manual of radon gas emission characteristics and techniques for estimating ventilating air requirements: Part 1. *CIM Bulletin,* **75**(845), pp. 149-156.

TIRMARCHE, M., HARRISON, J., LAURIER, D., BLANCHARDON, E., PAQUET, F. and MARSH, J., 2012. Risk of lung cancer from radon exposure: contribution of recently published studies of uranium miners. *Annals of the ICRP,* **41**(3-4), pp. 368-377.

TIRMARCHE, M., LAURIER, D., BOCHICCHIO, F., CARDIS, E., BINKS, K., HOFMANN, W., MUIRHEAD, C. and CANU, I., 2010. *Alpha Risk – Final Scientific Report – Version 2.0. Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiological studies, organ dose calculation and risk assessment.* Project No. 516483. France: European Commission, Community Research and Development Information Service.

TIRMARCHE, M., RAPHALEN, A., ALLIN, F., CHAMEAUD, J. and BREDON, P., 1993. Mortality of a cohort of French uranium miners exposed to relatively low radon concentrations. *British journal of cancer,* **67**(5), pp. 1090-1097.

TOMASEK, L., 2014. Effect of age at exposure in 11 underground miners studies. *Radiation Protection Dosimetry,* **160**(1-3), pp. 124-127.

TOMASEK, L., 2013. Lung cancer risk from occupational and environmental radon and role of smoking in two Czech nested case-control studies. *International journal of environmental research and public health,* **10**(3), pp. 963-979.

TOMASEK, L., 2012. Lung cancer mortality among Czech uranium miners-60 years since exposure. *Journal of radiological protection: Official journal of the Society for Radiological Protection,* **32**(3), pp. 301-314.

TOMASEK, L., 2011. Interaction of radon and smoking among Czech uranium miners. *Radiation Protection Dosimetry,* **145**(2-3), pp. 238-242.

TOMASEK, L., 2002. Czech miner studies of lung cancer risk from radon. *Journal of radiological protection : official journal of the Society for Radiological Protection,* **22**(3A), pp. A107-12.

TOMASEK, L. and DARBY, S.C., 1995. Recent results from the study of West Bohemian uranium miners exposed to radon and its progeny. *Environmental health perspectives,* **103 Suppl 2**, pp. 55-57.

TOMASEK, L., DARBY, S.C., FEARN, T., SWERDLOW, A.J., PLACEK, V. and KUNZ, E., 1994. Patterns of lung cancer mortality among uranium miners in West Bohemia with varying rates of exposure to radon and its progeny. *Radiation research,* **137**(2), pp. 251-261.

TOMASEK, L., DARBY, S.C., SWERDLOW, A.J., PLACEK, V. and KUNZ, E., 1993. Radon exposure and cancers other than lung cancer among uranium miners in West Bohemia. *Lancet,* **341**(8850), pp. 919-923.

TOMASEK, L., ROGEL, A., TIRMARCHE, M., MITTON, N. and LAURIER, D., 2008. Lung cancer in French and Czech uranium miners: Radon-associated risk at low exposure rates and modifying effects of time since exposure and age at exposure. *Radiation research,* **169**(2), pp. 125-137.

TOMASEK, L., SWERDLOW, A.J., DARBY, S.C., PLACEK, V. and KUNZ, E., 1994. Mortality in uranium miners in west Bohemia: a long-term cohort study. *Occupational and environmental medicine,* **51**(5), pp. 308-315.

TURNER, M.C., KREWSKI, D., CHEN, Y., POPE, C.A.,3rd, GAPSTUR, S. and THUN, M.J., 2011. Radon and lung cancer in the American Cancer Society cohort. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* **20**(3), pp. 438-448.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES., 2014. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General.* Atlanta, GA: U.S.: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health,.

UNITED NATIONS, 2012. *Biological mechanisms of radiation actions at low doses. A white paper to guide the Scientific Committee's future programme of work.* New York: United Nations.

UNITED NATIONS, 2010. *Effects of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation; UNSCEAR 2008 Report to the General Assembly with Scientific Annexes: Annex A and B.* New York: United Nations.

UNITED NATIONS, 2009. *Effects of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation; UNSCEAR 2006 Report to the General Assembly with Scientific Annexes. Volume II. Scientific Annexes C, D and E.* New York: United Nations.

UNITED NATIONS, 2008. *Effects of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation; UNSCEAR 2006 Report. Volume I. Report to the General Assembly with Scientific Annexes. Scientific Annexes A and B: Epidemiological studies of radiation and cancer; Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure.* New York: United Nations.

VACQUIER, B., CAER, S., ROGEL, A., FEURPRIER, M., TIRMARCHE, M., LUCCIONI, C., QUESNE, B., ACKER, A. and LAURIER, D., 2008. Mortality risk in the French cohort of uranium miners: extended follow-up 1946-1999. *Occupational and environmental medicine,* **65**(9), pp. 597-604.

VACQUIER, B., RAGE, E., LEURAUD, K., CAER-LORHO, S., HOUOT, J., ACKER, A. and LAURIER, D., 2011. The influence of multiple types of occupational exposure to radon, gamma rays and long-lived radionuclides on mortality risk in the French "post-55" sub-cohort of uranium miners: 1956-1999. *Radiation research,* **176**(6), pp. 796-806.

VACQUIER, B., ROGEL, A., LEURAUD, K., CAER, S., ACKER, A. and LAURIER, D., 2009. Radon-associated lung cancer risk among French uranium miners: modifying factors of the exposure-risk relationship. *Radiation and environmental biophysics,* **48**(1), pp. 1-9.

VAN DILLEN, T., DEKKERS, F., BIJWAARD, H., BRUSKE, I., WICHMANN, H.E., KREUZER, M. and GROSCHE, B., 2016. Modeling Lung Carcinogenesis in Radon-Exposed Miner Cohorts: Accounting for Missing Information on Smoking. *Risk analysis : an official publication of the Society for Risk Analysis,* **36**(5), pp. 954-967.

VAN DILLEN, T., DEKKERS, F., BIJWAARD, H., KREUZER, M. and GROSCHE, B., 2011. Lung cancer from radon: a two-stage model analysis of the WISMUT Cohort, 1955-1998. *Radiation research,* **175**(1), pp. 119-130.

VILLENEUVE, P.J., LANE, R.S. and MORRISON, H.I., 2007. Coronary heart disease mortality and radon exposure in the Newfoundland fluorspar miners' cohort, 1950-2001. *Radiation and environmental biophysics,* **46**(3), pp. 291-296.

VILLENEUVE, P.J., MORRISON, H.I. and LANE, R., 2007. Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. *Health physics,* **92**(2), pp. 157-169.

WALSH, L., DUFEY, F., TSCHENSE, A., SCHNELZER, M., GROSCHE, B. and KREUZER, M., 2010. Radon and the risk of cancer mortality--internal Poisson models for the German uranium miners cohort. *Health physics,* **99**(3), pp. 292-300.

WALSH, L., DUFEY, F., TSCHENSE, A., SCHNELZER, M., SOGL, M. and KREUZER, M., 2012. Prostate cancer mortality risk in relation to working underground in the Wismut cohort study of German uranium miners, 1970-2003. *BMJ open,* **2**(3), pp. 10.1136/bmjopen-2012-001002. Print 2012.

WALSH, L., GROSCHE, B., SCHNELZER, M., TSCHENSE, A., SOGL, M. and KREUZER, M., 2015. A review of the results from the German Wismut uranium miners cohort. *Radiation Protection Dosimetry,* **164**(1-2), pp. 147-153.

WALSH, L., TSCHENSE, A., SCHNELZER, M., DUFEY, F., GROSCHE, B. and KREUZER, M., 2010. The influence of radon exposures on lung cancer mortality in German uranium miners, 1946-2003. *Radiation research,* **173**(1), pp. 79-90.

WELCH, K., HIGGINS, I., OH, M. and BURCHFIEL, C., 1982. Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. *Archives of Environmental Health,* **37**(6), pp. 325-335.

WHO, October, 2014-last update, Radon and health [Homepage of World Health Organization], [Online]. Available: http://www.who.int/mediacentre/factsheets/fs291/en/ [December, 2015].

WHO, 2009. *WHO handbook on indoor radon: a public health perspective.* Geneva, Switzerland: World Health Organization.

WHO, 2006. *Report on the 2nd meeting of the WHO International Radon Project. WHO Headquarters, Geneva, 13-15 March 2006. Edited by Hajo Zeeb.* Geneva, Switzerland: World Health Organization.

WHO, 1998. *International Classification of Diseases, Ninth Revision (ICD-9).* Geneva, Switzerland: World Health Organization.

WOODWARD, A., RODER, D., MCMICHAEL, A.J., CROUCH, P. and MYLVAGANAM, A., 1991. Radon daughter exposures at the Radium Hill uranium mine and lung cancer rates among former workers, 1952-87. *Cancer causes & control : CCC,* **2**(4), pp. 213-220.

WORLD NUCLEAR ASSOCIATION, March, 2017-last update, Country Profiles [Homepage of World Nuclear Association], [Online]. Available: http://www.world-nuclear.org/info/country-profiles/ [04/15, 2017].

WORLD NUCLEAR ASSOCIATION, November, 2016-last update, Country Profiles [Homepage of World Nuclear Association], [Online]. Available: http://www.world-nuclear.org/info/country-profiles/ [11/9, 2016].

XUAN, X.Z., LUBIN, J.H., LI, J.Y., YANG, L.F., LUO, A.S., LAN, Y., WANG, J.Z. and BLOT, W.J., 1993. A cohort study in southern China of tin miners exposed to radon and radon decay products. *Health physics,* **64**(2), pp. 120-131.

ZABLOTSKA, L.B., LANE, R.S. and FROST, S.E., 2013. Mortality (1950-1999) and cancer incidence (1969-1999) of workers in the Port Hope cohort study exposed to a unique combination of radium, uranium and gamma-ray doses. *BMJ open,* **3**(2), pp. 10.1136/bmjopen-2012-002159. Print 2013.

ZABLOTSKA, L.B., LANE, R.S., FROST, S.E. and THOMPSON, P.A., 2014. Leukemia, lymphoma and multiple myeloma mortality (1950-1999) and incidence (1969-1999) in the Eldorado uranium workers cohort. *Environmental research,* **130**, pp. 43-50.